DOLON

Addressing unmet needs in extremely rare and paediatric-onset diseases: how the biopharmaceutical innovation model can help identify current issues and find potential solutions

Prepared by Dolon Ltd
www.dolon.com

Emilie Neez
Arianna Gentilini
Adam Hutchings

Prepared for the European Federation of Pharmaceutical Industry Associations (EFPIA)

This report derives from an EFPIA workshop with Senior Leadership members to tackle the issue of unmet needs in extremely rare and paediatric-onset diseases.

Introduction

The Regulation on Orphan Medicinal Products (henceforth 'OMP Regulation') was introduced in 2000 by the European Commission to stimulate investment in the development of medicinal products for rare diseases by creating incentives for manufacturers. Orphan market exclusivity (OME), distinct regulatory processes, as well as scientific and financial assistance for research and development (R&D) were instituted. Similarly, the Regulation on medicinal products for paediatric use ('Paediatric Regulation') was enacted in 2006 to bolster investigation and development of medicinal products for the paediatric population. The Regulation introduced an obligation to design and complete a Paediatric Investigation Plan (PIP, unless waived), and rewards for fulfilling this obligation in the form of extended intellectual property protection.

Both Regulations have been a great success, progressing care in many overlooked conditions. Approximately half of the innovation seen in rare diseases since 2000 can be attributed to the advent of the OMP Regulation (Dolon, 2020). The Paediatric Regulation contributed to significantly expanding research in children, hence increasing the number of medicines authorised for children and enhancing paediatric-specific expertise (Technopolis Group, 2016).

Despite this progress, concerns about remaining unmet needs, patient access, affordability, and sustainability of pharmaceutical spending have risen in the past few years. In particular, there are concerns about the appropriateness of the current regulatory framework to attain the societal goal of reducing unmet needs while ensuring value-for-money.

As a result, the European Commission is examining the strengths and shortcomings of both Regulations, with the view to recalibrate policy. EFPIA supports the intention to ensure that policy tools are adequately tailored and efficient to meet patients' needs. At the same time, there is a need to carefully consider how policy changes may affect the amount and direction of innovation, which have a consequential impact for patients. Therefore, potential regulatory changes should recognize the dynamics of investment (i.e., the broader factors that influence investment decisions), which influence the innovation that accrues.

This report summarises the contents of an EFPIA workshop which gathered Senior staff from member company R&D, Clinical, Strategy, and Commercial functions to tackle the issue of unmet medical needs in rare and paediatric diseases. It first describes an explanatory framework that illustrates how biopharmaceutical companies make investment decisions, taking into account scientific, commercial, and policy factors[1]. Applying this framework, the report then examines the hurdles that have impeded innovation in two 'white spots' where limited treatments are available: extremely rare diseases and paediatric-onset diseases. Finally, this report outlines ways forward towards lowering unmet needs in those white spots.

[1] The framework generalises investment decision-making processes, which in practice varies across companies.

1. The biopharmaceutical innovation model

Industry plays a central role in medicines development

Historically, the biopharmaceutical industry has been the most important actor in developing, manufacturing, and commercialising medicines. Although the public sector plays an important role in shaping the scientific environment that paves the way for drug discovery and innovation to flourish, non-commercial organisations very rarely develop medicines to the point of marketing approval and do not have the necessary expertise to manufacture and commercialise approved medicines.

Governments and non-profit organisations routinely fund research in public institutions (e.g., universities, hospitals) that advance foundational science. Public funding supports basic research, as well as the development of disease knowledge and infrastructure. As such funding decisions taken by public sector organizations (e.g., the US National Institutes of Health (NIH)) impact the nature of innovation, as drug R&D is often stimulated by advances in basic science. Publicly funded academic research also operates through prioritisation processes that determine budget allocation, number of grants, and eventually academic careers.

However, it is largely the biopharmaceutical industry who bears the risk of formulating and trialling medicines in humans and finances expensive and lengthy clinical trials (Vital Transformation, 2021). A study of medicines which received NIH funding in 2000 and were approved by 2020 showed that "total private investment for the 18 approved medicines exceeded NIH funding by orders of magnitude: $44.2 billion in private investment compared to $670 million in NIH funding" (Vital Transformation, 2021). It takes on average 10 years to bring a drug to market from the first clinical trial in humans (Jayasundara et al., 2019), and requires hundreds of millions of dollars investment (Jayasundara et al., 2019; Wouters et al., 2020). In addition, failure rates are extremely high, with more than 85% of all medicines entering clinical testing never reaching successful approval (Wong et al., 2019).

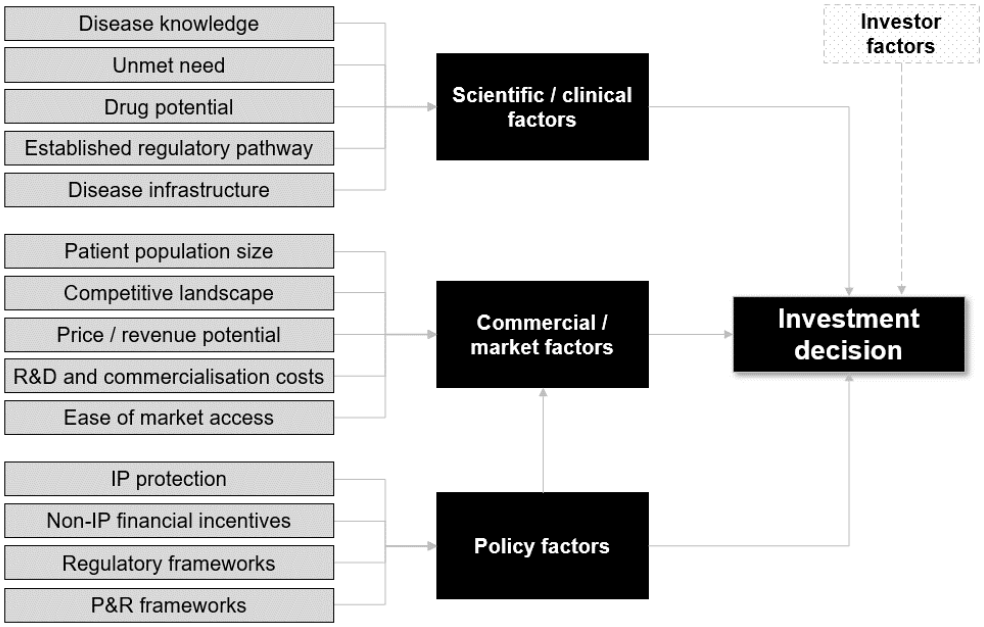
The amount and nature of pharmaceutical innovation therefore directly stem from a series of critical decisions taken both by public organisations and by private companies. The next section examines factors that affect research-based companies' R&D investment decisions, given the risk involved and capital required.

When making investment decisions, companies first consider the scientific opportunity, then examine commercial viability within the policy environment

More than 10,000 diseases have been identified worldwide to date (WHO, 2021), each of which represents potential investment options for biopharmaceutical companies. Therefore, companies need to carefully weigh investment decisions by assessing opportunities across multiple potential therapeutic targets (new treatments) and disease areas. Such decisions are usually made by high-level committees within biopharmaceutical company R&D functions, with senior representation from scientific, clinical, and commercial functions.

When biopharmaceutical companies make investment decisions, they take into account several internal and external factors, which broadly relate to scientific/clinical, commercial/market, and policy factors. These factors are illustrated in a simplified taxonomy of investment decisions below (**Error! Reference source not found.**).

Figure 1. Simplified taxonomy of investment decision factors (non-exhaustive)



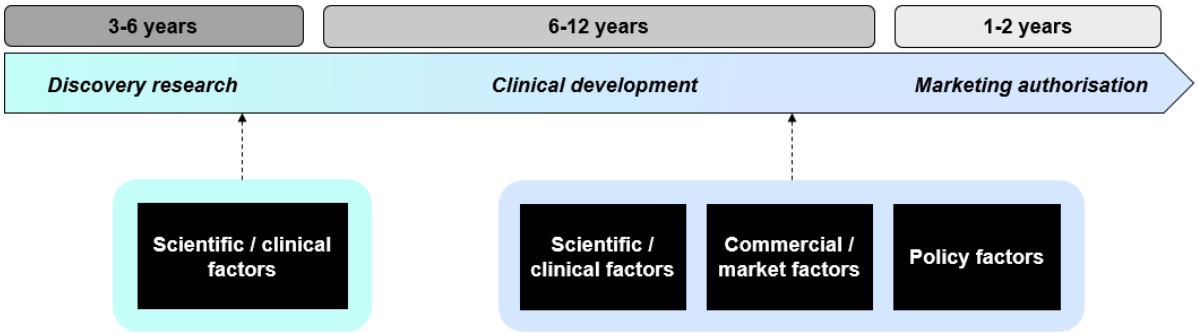
Scientific / clinical factors

Although all aforementioned factors feed into investment decisions, they are not equally important throughout all stages of development. At the early pre-clinical stage, investment decisions are mostly informed by scientific and clinical factors, such as the understanding of the pathophysiology of disease, the existence of promising drug targets, and the extent of unmet needs. Companies usually have therapeutic areas of specialism, where internal scientific knowledge and expertise are a competitive advantage and influence their assessment of the viability of developing medicines.

Patients and physicians also input to the investment decision. Companies work with patients and physicians to understand their needs and preferences for a novel therapy. They then assess whether patients' aspirations are scientifically feasible. Patients are further involved throughout the development process, for example, informing trial designs and influencing endpoint selection.

Only where clinical feasibility is demonstrated do companies consider additional factors, such as the commercial opportunity within the policy environment.

Figure 2. Role of investment factors by stages of drug development



Illustrative

Commercial / market factors

Commercial and market considerations directly impact the revenue potential of a new medicinal product. When a viable drug target has been identified, companies ask themselves how many patients might be eligible (population size) and what is society's willingness to pay for the value it brings (value-based price). They also need to consider whether a drug (or multiple drugs) for the same condition is (are) already on the market (or is/are expected to launch ahead of them) and how this might impact their market share.

When investigating price potential, companies seek to understand what payers are willing to pay for a product given the benefits it brings to patients and society. This includes looking at the added benefit provided by the new therapy and assessing prices of existing treatments for that condition, as well as prices of medicines with similar therapeutic benefits in other diseases. This process is undertaken across major international markets, because decisions to invest in medicine development are always considered globally. The price precedents that payers establish thus have a direct impact on decisions about which disease areas to invest in (and which areas will see innovation in future).

Commercialisation of a product requires considerable upfront and continuous investments. To meet regulatory requirements (i.e., demonstrate clinical efficacy and safety), companies need to fund rigorous and expensive clinical trials, whose outcomes are highly unpredictable (less than 7% of all orphan drug candidates reach approval (Wong et al., 2019)). In addition, the production of medicinal products requires large investments in pharmaceutical development and manufacturing capabilities. In particular, fulfilling Chemistry, Manufacturing and Control (CMC) requirements is onerous. Commercialisation activities, such as safety monitoring, regulatory and payer processes, distribution, and medical education, are also costly.

Policy factors

Ultimately, investment decisions are contingent on policy factors, which relate to the political and regulatory environment surrounding the medicine and disease. In particular, a reliable intellectual property (IP) system is necessary to ensure innovators are protected from immediate copy by generic companies, and thus that innovation is incentivised. The duration over which revenue is obtained for a medicine is largely determined by the length of patent and other forms of intellectual property protection (including supplementary protection certificate extension, regulatory data protection, and OME)[2]. Policy incentives other than IP protection are also sometimes used to reward innovation, such as tax credits, grant programmes, and other financial subsidies.

Investment decisions are also greatly influenced by regulatory and pricing and reimbursement (P&R) frameworks. It may be less economically viable to invest in a disease area where a clear approval pathway is missing or whose burden is not considered a priority by payers. Existence of international reference pricing, whereby countries formally or informally link drug prices to those in other countries, affects the overall revenue potential of a product and might ultimately lead to a negative decision to invest in a certain disease. Policy factors have a large impact on commercial factors, as they significantly affect a medicines' revenue potential.

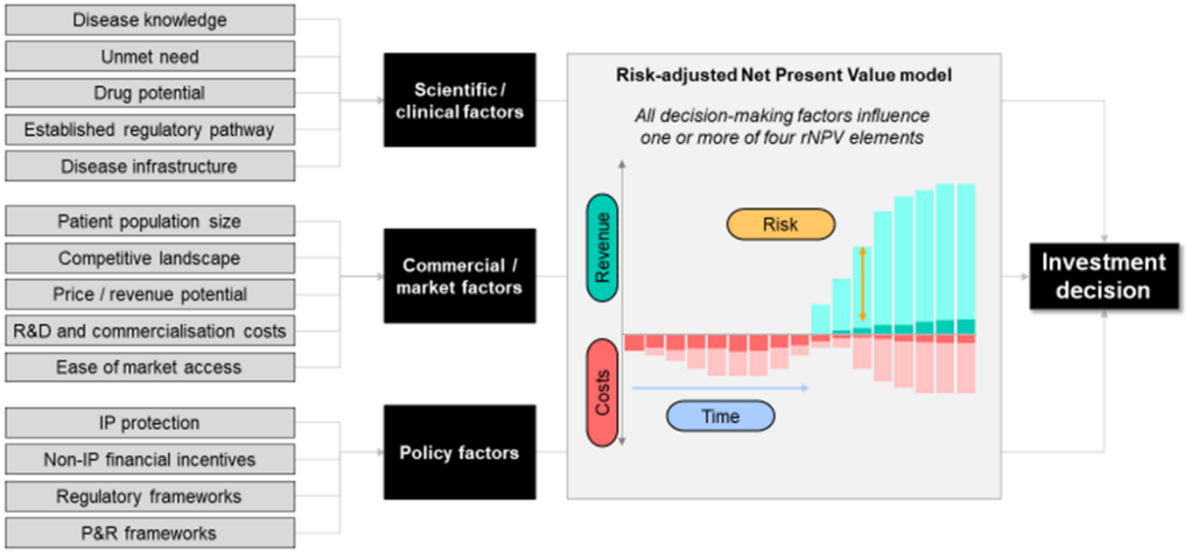
[2] Nevertheless, the actual level of revenue remains highly uncertain, partly due to the impact of competition from other treatments and of pricing frameworks. It has been assessed that about 8 out of 10 approved medicines are not commercially successful (i.e., never reach a level of revenue that matches average R&D spending) (Vernon, Golec and DiMasi, 2010).

Companies routinely rely on financial modelling to inform investment decisions

To support decision-making, companies routinely employ risk-adjusted net present value modelling (rNPV) or similar financial methods, which assess the economic viability of an early-stage medicine. rNPV modelling yields in a single figure the value today of all future cashflows (positive and negative) from a potential medicine and adjusts them for the high risk of development failure and cost of capital. At a high-level, it first estimates the net value of a product at each development timepoint based on future cash flows estimating costs (R&D and commercialisation) and revenue. Net value is then discounted, to account for the opportunity cost of capital, and risk-adjusted, to account for the risk of failure. Opportunities with higher rNPV are prioritised over those with lower rNPV, all other things being equal, and opportunities with negative rNPV are unlikely to be funded.

Decisions are revisited at each key stage of development ('go/no-go') based on revised forecasting incorporating new clinical data and developments in the commercial and policy landscape.

Figure 3. rNPV modelling role in investment decisions



Global dynamics are considered when making investment decisions

Drug investment decisions are global in nature: it rarely, if ever, makes sense to develop a medicine for a single country or region. Investment decisions therefore incorporate expected revenues and costs from all regions in which companies expect to launch. Multi-country analyses factor in global market and policy conditions. For example, research is usually undertaken to assess price potential and likely prescribing uptake.

Decisions about which assets to invest in and how to run the development programme reflect expectations of where the revenue is likely to come from. The US often accounts for approximately half of projected revenue, compared to approximately one quarter for Europe (EFPIA, 2020). As such, US policy frameworks have a greater impact on investment decisions. Albeit at a lower relative level, EU policy frameworks, such as the OMP and Paediatric Regulations, also affect investment decisions. For example, if a medicine only has market protection in Europe thanks to OME, the quarter of global revenue attributable to that region could make the difference between a negative and positive rNPV.

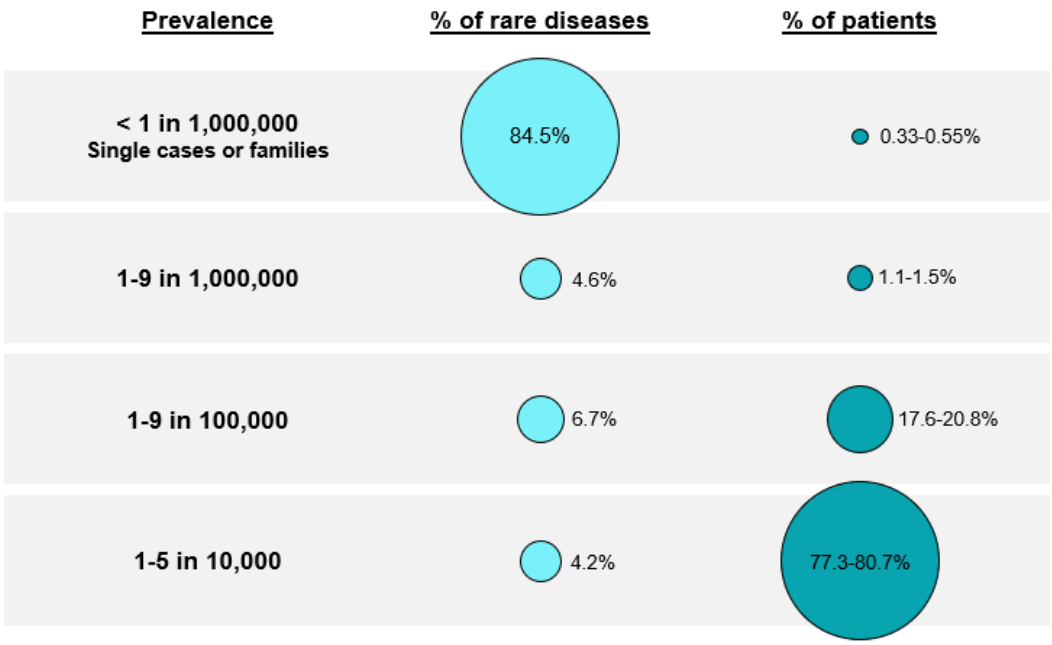
2. The case of extremely rare diseases

Most of the 95% of rare diseases without treatment options are extremely rare

European Commission publications have highlighted that 95% of the 6,000-7,000 identified rare diseases are without approved therapeutic options (European Commission, 2020). This lack of treatment in most rare diseases is interpreted as a major unmet medical need and a failure of the OMP Regulation to address these diseases. While it is true that most rare diseases remain improperly addressed, the full picture is more complicated.

Rare diseases encompass, by European definition, all diseases which affect fewer than 5 in 10,000 people. Yet this definition hides wide variations. Rare diseases are not uniformly spread across prevalence: only 4% of diseases sit in the 1-5 in 10,000 prevalence bracket, while 84% affect fewer than 1 in 1,000,000 patients (Wakap et al., 2020). While the more prevalent diseases are less frequent, the size of the populations suffering from each of these diseases is significantly higher, meaning that 80% of all rare disease patients fall in the ~150 diseases with the highest prevalence[3]. Therefore, from a utilitarian perspective, 4/5^{ths} of rare disease burden sits in these diseases. These are also the diseases where most research has been conducted and where the greatest disease understanding exists. Accordingly, these are the diseases in which most rare disease investment has occurred and where most orphan medicines have been approved.

Figure 4. Distribution of rare diseases and rare disease patients across prevalence levels



Not to scale *Adapted from Wakap et al., 2020*

The prevalence of the disease has a direct impact on both the clinical opportunity and economic viability of the investment decision. The rarer the disease, the more the scientific and commercial challenges inherent to rare disease therapeutic development are magnified.

The rest of this paper focuses on extremely rare diseases, defined henceforth as affecting fewer than 1 in 1,000,000 people. Few, if any, of those diseases have an approved treatment

[3] The paper focused on 3,585 diseases for which point prevalence was available.

option; most affect only a handful of individuals or families[4]. That is not to say, however, that more common rare diseases are less worthy of attention. Rare disease patients who benefit from available therapeutic options usually have remaining unmet needs, as a single product is almost never sufficient to resolve all patients' needs. Nevertheless, because extremely rare diseases have been identified as an investment 'white spot', their specific hurdles warrant dedicated attention.

There are significant hurdles to innovation in extremely rare diseases

The challenges to innovation in extremely rare diseases are many-fold.

Clinical opportunity

Innovation in extremely rare diseases is thwarted by enormous scientific challenges. For most of these diseases, fundamental research is effectively non-existent. Animal and cellular models, which are essential to medicine development, are rarely available. There are often no experts or research organisations focused on the disease. As a result, the pathophysiology of disease is seldom known. Even when the disease's underlying root cause is understood, viable drug targets are rarely identified. Without solid basic research to build on, translational research cannot be conducted, and industry is unable to identify promising medicines for development. Given the current state of knowledge of extremely rare diseases, few of them can conceivably see a therapy developed in the coming years.

Beyond pre-clinical research, scientific challenges manifest themselves during clinical development. It is hard to design and recruit clinical trials when patients are so few. Conducting an adequately powered trial might be statistically impossible. It may require enrolling most of the diagnosed patient population, thereby limiting potential commercial opportunity. The lack or insufficiency of diagnostic capabilities and treatment networks hamper patient identification and enrolment. Moreover, the absence of patient organisations hinders formal patient involvement in the trial design.

Economic viability

At prices that society is willing to pay, few (if any) products are economically viable with such small patient populations. There is a close inverse relationship between the size of the patient population and the price at which investment is viable. In other words, price must balance for the smallness of patient populations, accounting for the costs and risks of development. The volume opportunity may be more than 100,000 times lower than for common diseases. In addition, average R&D costs per patient (calculated from publicly available data on overall R&D costs and average number of participants in clinical trials (Jayasundara et al., 2019; Wouters et al., 2020)) are higher for orphan medicines than for non-orphan ones, even if total R&D expenditure is lower. The probability of success (from phase I) is also lower for orphan than non-orphan medicines (6.2% vs. 13.8%) (Wong et al., 2019). On balance the economic case is thus significantly worse in the rare disease space.

Research has evaluated the willingness-to-pay levels needed to provide the same investment proposition for rare diseases as for more common diseases (Berdud, Drummond and Towse, 2020). Using the United Kingdom's (UK) framework of cost per quality-adjusted life year (QALY), authors showed that society would need to be willing-to-pay nearly £1 million per QALY for ultra-rare populations to give the same return on investment as non-rare disease

[4] Strimvelis for ADA-SCID is an example of medicine approved for an extremely rare disorder, affecting approximately 0.02 in 10,000 people in the EU. Another example is Naglazyme, approved in mucopolysaccharidosis type VI (Maroteaux-Lamy syndrome), which affects between 0.0088 and 0.024 in 10,000 people in the EU.

medicines.[5] Importantly, this willingness-to-pay of £1 million per QALY is over three times higher than the current maximum cost-effectiveness threshold for very rare medicines in the UK (£300,000 per QALY), and fifty times higher than the threshold for non-orphan diseases (£20,000 per QALY).

P&R barriers compound scientific and commercial hurdles at every point along the medicine's journey to patients. Whilst misalignment on regulatory requirements between regions (in particular, between the FDA and EMA) is a challenge, a larger issue lies in the gap between Health Technology Assessment (HTA) bodies and regulators' evidentiary demands. HTA bodies routinely seek similar evidence standards for rare diseases as for non-rare ones, despite increased flexibility from regulators in light of clinical challenges. This discrepancy in evidence demands complicates already lengthy P&R negotiations. In addition, payers effectively set a cap on willingness-to-pay, and often deny reimbursement for medicines when innovators offer a price level to sustain future innovation. Payers may also restrict reimbursement to specific sub-populations, further limiting the treatable patient population and worsening the commercial opportunity. As a result, reimbursement processes are protracted and costly for an uncertain outcome; price negotiations are lengthy and risky.

In many instances, the availability of a new therapy is insufficient in itself to bring forward eligible patients. Manufacturers must work with physicians and healthcare systems to identify patients who might benefit. The difficulty in identifying treatable patients further decreases the volume opportunity and increases risk: even after a successful development and positive reimbursement outcomes, products may effectively fail to reach the targeted patients and therefore fail commercially.

Policy hurdles

While regulatory processes have been adapted to recognise the challenges associated with small populations, CMC requirements have not. Even in the case of accelerated access approaches for diseases with high unmet need, there are limited opportunities for accelerated CMC development (EFPIA and EBE, 2017). The level of investment in CMC is disproportionate compared with the size of the patient population, especially considering that economies of scale are less likely to be achievable in small populations.

Being able to manage the tremendous complexity of regulatory and P&R processes, to meet CMC requirements, and to deliver orphan medicines all the way to the patient may require, in some companies, to establish structures dedicated to rare diseases. To be successful, companies must prioritise resources and build expertise towards navigating institutional processes. This creates an important barrier to entry for many pharmaceutical companies.

Taken together, the scientific and commercial barriers, compounded by structural barriers, mean that return on investment is consistently negative in very rare diseases. In addition, some companies are deterred from investing in the extremely rare disease space for fear of negative reputational impact as a result of having to charge high prices with the potential for restricted patient access. Because prices are usually presented without context in the press, and the extent of the scientific and commercial challenges to R&D are unrecognised, prices are misconstrued and negatively affect company investment decisions.

Lastly, the Paediatric Regulation mandates investigating in children a medicine in development in adult populations (unless a waiver is obtained). As a result, challenges to the

[5] The authors defined ultra-rare as less than 0.2 in 10,000 people, which is a population 20 times larger than the extremely rare diseases of interest in this paper.

development of medicines in paediatric indications augment the aforementioned hurdles to innovation in extremely rare diseases.

A set of interdependent solutions must be put in place through strong collaboration

The extent and diversity of challenges in researching and developing medicines and solutions to address extremely rare diseases warrant multi-faceted solutions. Policymakers should be fully aware of the significance of challenges and the amount of effort needed to surmount them. No single solution stands to meaningfully stimulate development. Instead, a set of interdependent solutions must be implemented and funded in a collaborative fashion.

Moonshot mindset

No medicine can be developed without strong scientific grounds. For extremely rare diseases, a 'moonshot' mindset should be adopted to overcome existing significant scientific barriers, whereby stakeholders work together towards the shared goal of breaking ground.

More specifically, the 'moonshot' initiative would entail committing significant public funding for basic research and infrastructures in very rare diseases, potentially through European Reference Networks. Europe-wide patient registries should be set up to track the natural history of these diseases, as well as characterise burden and unmet needs. These registries could be the product of collaboration between policymakers, hospitals, patients, and industry. Investments in research and deployment strategies are also needed to shorten the path to diagnosis (for instance through new-born screenings, deep phenotyping).

Because funding is limited while extremely rare diseases are numerous, stakeholders could agree on a priority list of extremely rare diseases (based on criteria to be determined) towards which investment would be focused in the first instance. The list could be updated as progress is made, hence adopting a sequential approach to tackling needs. The list would be voluntary in nature; that is, stakeholders would be invited to work in selected disease areas, without being mandated or compelled to by restricting incentives to prioritised areas. Nevertheless, it should be noted that defining a priority list may have drawbacks, such as diverting funding away from non-prioritised diseases.

Breaking barriers

Breakthrough science is a necessary but non-sufficient condition to addressing unmet needs. Existing institutional barriers must be addressed for future innovation to reach patients.

Regulatory approval could be reconfigured to accommodate both the challenges of extremely rare diseases and the promises of novel science. A central issue for the development of medicines in extremely rare diseases is the limited number of patients. Consequently, any way to increase the number of patients treated with a therapy stands to increase the probability of development. It is thus beneficial to encourage the development of medicines across multiple rare indications and indication expansions from common diseases to rarer ones. Beyond the current paradigm, platform-based approaches could be considered, whereby development no longer focuses on discrete indications but on improving groups of diseases with the same or similar root causes. This would necessitate a significantly different regulatory mindset, as well as adaptation of P&R processes (as price decreases currently associated with indication expansions would prevent the broad adoption of these platforms).

P&R frameworks also need to be transformed for extremely rare diseases. Future frameworks should increase manufacturers' confidence that medicines will be reimbursed for all eligible patients: the point is that the risk taken by developers should be lowered and the possibility to recoup initial investment heightened. Principles to guide the calibration of P&R systems for

rare diseases in Europe have been proposed by the ORPH-VAL group (Annemans et al., 2017). In particular, payers should exhibit a flexibility on par with that of regulators. An example of changes to P&R systems could be the more widespread adoption of the French model of cohort *authorisation temporaire d'utilisation* (ATUs), which allows patient access ahead of HTA, with the view to fasten access.

More significant reforms could be considered, such as the introduction of reimbursement guarantees (i.e., ensuring that all orphan-designated products are automatically reimbursed, like in Germany), early alignment on a plausible price, and even prize-like schemes (i.e., lump sum of money attributed for the successful development of a medicine, independent of patient numbers; although it should be noted that prizes would likely need to be sizeable to positively improve the investment equation, and would fail to create a sustainable R&D effort beyond the first approved product).

In addition, CMC requirements should be made more manageable and proportionate to the patient population size. In order to achieve the goal of faster and better patient access, changes to the traditional CMC development paradigm are needed. EFPIA and European Biopharmaceutical Enterprises (EBE) have published guiding principles and suggestions for streamlining the CMC process in specific cases (EFPIA and EBE, 2017).

Other critical changes are needed. For example, patient identification programmes should systematically be developed when medicines get approved, though collaboration between manufacturers and health systems. All in all, the 'moonshot' mentality must be shared by all stakeholders (not least payers) if innovation is to be sustainable.

Policy pulls

Establishing meaningful financial incentives may also support development decisions. While they would not directly help with scientific challenges, these incentives could improve the economic viability of medicine development. The extent to which they may change investment decisions depends on the value of incentives. Therefore, a voucher (e.g., that would provide earlier market access or market exclusivity) that can be traded would likely have a much higher value than one specific to an orphan medicinal product. In all cases, curtailing OMP incentives currently available under the 1-5 per 10,000 orphan definition stands to only have a negative impact on innovation while not addressing the set of challenges presented by ultra-rare diseases.

Industry will likely be unable to address all unmet needs

Even with all the above changes in place, industry will realistically be unable to develop medicines for all 6,000-7,000 rare diseases. Distinction should be made between diseases where industry can lead on the development of medicines (e.g., where basic science exists and the current development paradigm can work), and other diseases, where other development models (e.g., development by non-profits) may be warranted.

In much the same way that industry itself cannot solve all issues, it is unlikely that Europe in isolation can have an impact large enough to change the R&D equation. Nevertheless, improvements, however small on a global scale, can help.

Still, there is cause for optimism. Twenty years ago, the scientific and commercial challenges in rare diseases seemed just as daunting than the ones currently faced by extremely rare diseases. Yet scientific progress, increased payer willingness-to-pay, higher regulatory flexibility and the advent of the OMP Regulation contributed to make orphan investment clinically and economically viable. This resulted in the over 160 orphan medicines we have

today, which have had a profound impact on the rare disease patients who access them. Addressing extremely rare diseases represents the next frontier, and while it will undoubtedly require further efforts on the same dimension, it is a worthy goal.

3. The case of paediatric-onset diseases

Difficult science, counterproductive regulatory requirements, and insufficient value recognition thwart innovation in paediatric-onset diseases

As for extremely rare diseases, reasons for the paediatric 'white spot' are multi-faceted and cover scientific challenges and institutional barriers.

First, studying paediatric-onset diseases is difficult. Most paediatric-onset diseases have a complex and poorly understood pathophysiology. As a result, basic knowledge of the disease and potential drug targets are often missing. The design and conduct of clinical trials are significantly more complicated than for adults. That is because children grow and their physiology changes over the trial duration (requiring trials to include multiple age groups in many diseases), ethical requirements are understandably more stringent, and endpoints or quality of life measures are not validated for children.

Secondly, regulatory requirements do not support efficient and targeted development. The Paediatric Regulation by design obliges paediatric developments for products for which adult development is underway. This results in development of medicines for children which are mainly adult driven and poorly reflect paediatric unmet needs. Although well-intentioned, the requirements set by the EMA Paediatric Committee (PDCO) can be burdensome, inconsistent over time, and inflexible, increasing costs and risks borne by manufacturers. For example, PDCO requires companies to submit detailed paediatric investigation plans (PIPs) very early in the development of a new medicine, which increases the chances that the development plan must be suspended or modified along the way. PDCO requirements are also often misaligned with those of regulatory agencies in other jurisdictions, further delaying the development and launch of paediatric medicines. This is particularly acute for a paediatric-onset disease where the PDCO expects to review and influence the full development plan. The Paediatric Regulation rewards companies that comply with PIPs, but the value of such rewards is linked to the adult development.

Thirdly, payers often fail to recognise the full extent of the value brought by paediatric medicines, even though the development of medicines for children is formally obliged (on-patent) or incentivised (off-patent) at regulatory level. The disease burden imposed on children and their carers, such as the time lost from school and from work, is improperly considered in HTAs. Such evaluations rarely account for the medicine's value to society as a whole.

Regulatory requirements should be reshaped and value better acknowledged

Industry has demonstrated its willingness to address paediatric needs by actively completing PIPs in compliance with the 2006 Paediatric Regulation, hence increasing the availability of and evidence for paediatric medicines (European Commission, 2020). Nevertheless, possibilities could be widened by limiting inefficiencies in the regulatory system and enhancing the reward for paediatric development.

First, regulatory requirements should be re-examined, to ensure that paediatric development can be streamlined and targeted. The interactions with and requirements set by PDCO should be significantly reshaped, towards a process that is clear and manageable for all stakeholders. There should be better alignment of regulatory requirements with those in other regions (e.g.,

the US) and between requirements of HTA bodies and with those of regulators. Joint consultations involving all stakeholders could be established to that effect.

Second, the value of paediatric medicines should be consistently recognised. A dialogue should be opened with all public budget holders (e.g., Ministry of Health, of Labour and of Economy) to better gauge the societal burden of paediatric diseases and the value of the benefits brought by novel therapeutic options. In addition, conversations with payers should be held to address the misalignment between regulatory and national-level incentives.

Finally, paediatric medicines could be automatically reimbursed from the point of approval (at the same price as adult medicines), ensuring speedy access to patients.

Conclusion

In summary, science, economics, and policy coalesce to inform investment decisions. It follows that these three dimensions must be addressed in concert for innovation to flourish in extremely rare and paediatric-onset diseases. Stakeholders must share a 'moonshot' mindset to foster scientific breakthroughs, abate existing barriers (including regulatory and P&R hurdles), and develop well-calibrated incentives. Change in the rare disease and paediatric spaces should be geared towards agile collaboration frameworks that allow meaningful partnerships towards the shared goal of reducing unmet needs. Changing the paediatric space will benefit all rare disease populations.

References

Annemans, L., Aymé, S., Le Cam, Y. *et al.* Recommendations from the European Working Group for Value Assessment and Funding Processes in Rare Diseases (ORPH-VAL). *Orphanet J Rare Dis* **12**, 50 (2017).

Berdud, M., Drummond, M. & Towse, A. Establishing a reasonable price for an orphan drug. *Cost Eff Resour Alloc* **18,** 31 (2020).

Dolon. Estimated impact of EU Orphan Regulation on incentives for innovation. (2020) [online] Available at: https://dolon.com/dolon/wp-content/uploads/2020/10/Estimated-impact-of-EU-Orphan-Regulation-on-incentives-for-innovation.pdf. Accessed on 04 June 2021.

EFPIA. The Pharmaceutical Industry in Figures. (2020) [online] Available at: https://efpia.eu/media/554521/efpia_pharmafigures_2020_web.pdf. Accessed 24 June 2021.

EFPIA and EBE. White Paper on Expedited CMC Development: Accelerated Access for Medicines of Unmet Medical Need – CMC Challenges and Opportunities (Final version). (2017) [online] Available at: EFPIA-EBE White Paper - Expedited CMC Development-Accelerated Access for Medicines of Unmet Medical Need - December 2017. Accessed 24 June 2021.

European Commission. Commission Staff Working Document Evaluation. Joint evaluation of Regulation (EC) No 1901/2006 of the European Parliament and of the Council of 12 December 2006 on medicinal products for paediatric use and Regulation (EC) No 141/2000 of the European Parliament and of the Council of 16 December 1999 on orphan medicinal products. (2020) [online] Available at: https://ec.europa.eu/health/sites/default/files/files/paediatrics/docs/orphan-regulation_eval_swd_2020-163_part-1.pdf. Accessed on 04 June 2021.

Jayasundara, K., Hollis, A., Krahn, M., *et al*. Estimating the clinical cost of drug development for orphan versus non-orphan drugs. *Orphanet J Rare Dis* **14**(1),12 (2019).

Nguengang Wakap, S., Lambert, D.M., Olry, A. *et al.* Estimating cumulative point prevalence of rare diseases: analysis of the Orphanet database. *Eur J Hum Genet* **28,** 165–173 (2020).

Technopolis Group. Study on the economic impact of the Paediatric Regulation, including its rewards and incentives. Final Report, SANTE/2015/D5/023 (2016)

Vernon, J., Golec, J., & DiMasi, J. Drug development costs when financial risk is measured using the Fama-French three-factor model. *Health economics* **19**(8), 1002-5 (2010).

VitalTransformation. Who Develops Medicines? An Analysis of NIH Grants. (2021) [online] Available at: http://vitaltransformation.com/wp-content/uploads/2021/05/V.T.-NIH-Grants-Analysis-5-10-2021_FINAL_v4.pdf. Accessed on 24 June 2021.

WHO. International Classification of Diseases (ICD-10). [online] Available at: https://www.who.int/standards/classifications/classification-of-diseases. Accessed 24 June 2021.

Wong, C.M., Siah, K.W. & Lo, A.W. Estimation of clinical trial success rates and related parameters, *Biostatistics* **20**(2), 273–286 (2019).

Wouters, O.J., McKee & M., Luyten, J. Estimated Research and Development Investment Needed to Bring a New Medicine to Market, 2009-2018. *JAMA* **323**(9), 844–853 (2020).