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How did we get here and where do we go now?
An economist's perspective on EU orphan drug policy.

Adam Hutchings

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Raising awareness about rare diseases and their impact on patients' lives

Introduction

On the 19th of May 2020, Zolgensma – a treatment for spinal muscular atrophy, a paediatric neuromuscular disease – became the fifteenth cell or gene therapy to gain approval from the European Medicines Agency. Twenty years after the advent of the European (EU) Orphan Regulation, a futuristic technology offered a life changing opportunity to patients suffering from a severe rare disease with few treatment options.

At the same time, the European Commission was putting the finishing touches to its Staff Working Document on the case for revising European orphan regulation, with the potential to repeal or scale-back central tenets of the legislation. Hence, at one of the moments of greatest scientific hope for patients with rare diseases, policymakers were considering the fate of the regulation that has seemingly been instrumental in their origination.
How did it come to this?

The divergence between the rapid pace of scientific progress in rare diseases and declining sentiment towards orphan medicines reflects a paradox that is at the heart of the European orphan drug debate. While the last twenty years have witnessed a sharp increase in the authorisation of orphan medicines, and the greatest scientific innovation of any sector of the biopharmaceutical industry, it has also become an embodiment of the concerns of politicians, policymakers, payers, as well as patients and physicians, about the same biopharmaceutical industry model that has spawned these innovations.

The prosecution's case can be summarised as follows:

- Orphan drug prices are too high and unsupported by the demonstrated value
- Patient access to orphan medicines has been slow and inadequate, especially beyond the major European markets (and within them: in France, the average delay between marketing authorisation and reimbursement decision is 618 days for orphans (EFPIA, 2020))
- Unmet need has been insufficiently reduced, with innovation clustered in a relatively small number of diseases
- Manufacturers have exploited monopoly power and gamed incentives to generate excessive profits
- The growing level of expenditure on orphan drugs is unaffordable.

To the regulation's detractors, the orphan drug innovation model is thus unfair, inefficient, and unsustainable.

My own opinions on this topic are more nuanced. Having started my career in the biopharmaceutical industry at the turn of the last millennium, and having specialised in the economics of orphan medicines for a good chunk of the time since, the maturing of the regulation and my maturing as an industry professional have run in parallel. On balance, I feel the regulation has aged better.

This document presents an informal, lightly referenced, and shamelessly self-referential account of my personal thoughts on the themes above. I begin with an overview of the orphan drug business model – in my belief, this is central to the policy conundrum. In the subsequent four sections I address some of the key challenges levelled at the orphan innovation model: price, access and unmet need, incentives, and sustainability. I conclude with some thoughts on how we might progress from here.

At its heart, this paper is a political-economic assessment of the challenges to ensuring that orphan drugs continue to be developed for rare diseases and reach all the patients who need them. It is a high-level look at the way our industry works within the legal, regulatory, and economic frameworks that policymakers create. My ambition is to step back from the specifics of individual products, companies, and countries and instead consider how incentives, systems, and business models come together to determine the amount and nature of innovation in rare diseases.

For medicines to improve human lives requires only two things: great science and good policy. The bench scientists have fulfilled their end of the bargain – now it's time for us social scientists to step up.

1. An overview of the orphan drug business model

Biopharmaceutical innovation has scientific, economic, and moral components

The starting point for any assessment of orphan policy ought to be a thorough understanding of the innovation model of medicines for rare diseases. Unfortunately, the biopharma innovation model is a poorly understood thing, and those of us in the industry must accept some blame for failing to explain it adequately to the rest of the world.

By 'innovation model', I mean the way that private companies make decisions and investments, within the constraints imposed by policymakers and market forces, that ultimately determines how many medicines are developed and in which diseases.

Most people would agree that getting this model right is a very important matter. Over the last 100 years, medicines have contributed greatly to the improvement in human health and wellbeing, and each of us has observed that benefit in our own lives and those of our families. No one is arguing that the existing medicines are unnecessary, nor that there isn't still a need for new ones. Rather, the question is how best to deliver this innovation.

Should such important work be left to the private sector? After all, in many countries other critical health services are provided by governments. And while the great majority of medicines approved in the last 50 years have come from corporations, Covid vaccines have shown that it is possible for public bodies to be involved in drug development.

Nevertheless, the private vs. public debate on medicines is largely an intellectual one. There is no realistic pathway for a wholesale nationalisation of the pharmaceutical industry, and many good reasons why it would not be desirable. Instead, we exist in a paradigm where (in broad brushstrokes) public institutions perform the basic research, private companies handle drug development and commercialisation, and governments heavily regulate all aspects of the process.

As private entities, companies have a fiduciary duty to generate shareholder value, a legal responsibility to comply with all relevant global legislation, and a moral duty to act in the best interests of patients and society. The business model therefore has both an economic and

moral component, on top of the scientific backbone of innovation, and the role of management is to balance these (sometimes competing) interests.

To date, a lot of attention has focused on the science of drug development or the perceived morality of corporate behaviour. Much less has been devoted to understanding the economics of investment decisions. That is problematic: societal goals will only be attained if economic incentives are correctly aligned. The focus of this discussion will therefore be on the economic component of the business model.

Patents, marketing authorisation, and pricing & reimbursement (P&R) rules create 'incentive frameworks' for companies

Central to economic incentives are profits. The financial return that companies obtain from their medicines is determined by a combination of market factors and incentive frameworks. Market factors include patient numbers, prescriber/patient preferences, competitor behaviour, supply constraints, price competition, guidelines, and economic conditions.

Incentive frameworks – established by politicians, regulators, and payers – comprise of intellectual property (IP) legislation, regulatory approval, P&R rules, and mandates governing marketing, manufacturing, and research. While such regulations can be burdensome, the drug industry relies on the licenses and protections created by these systems. These incentive frameworks are usually devised and overseen by governmental or quasi- governmental organisations and (ideally) explicitly or implicitly reflect societal priorities, values, and trade-offs.

Both the nature of the incentive framework and its relative importance versus market factors vary across countries. For example, in the United States (US) market factors play a bigger role in determining price and revenue than in Europe.

While these systems are mostly country-specific, the pharmaceutical industry is global. When making investment decisions, companies aggregate the expected revenues from across countries. Therefore, the incentive frameworks of the largest markets, such as the US, Japan, and Germany, have the greatest impact on company investment decisions.

The level of investment and innovation is determined by companies' business models within these frameworks

The biopharmaceutical business model is defined by three key characteristics: a large upfront investment in R&D, long time-lags between investment and return, and a high risk of failure. Decisions to invest in new medicines are therefore very complex and subject to great uncertainty.

Typically, companies assess the economic component of these decisions using some variant of a risk-adjusted net present value (rNPV) modelling approach. To simplify, this approach entails synthesising five key elements: the costs of development and commercialisation, the time from investment decision to approval, the potential future global revenue (if the product reaches the market), the probability of successfully obtaining a marketing authorisation, and the cost of capital. rNPV models condense these elements into a single figure. The rNPV is heavily influenced by incentives frameworks and market factors.

Crudely, the more positive the rNPV, the better the investment proposition. At each stage of the development process, companies adjust rNPV models to reflect the evolving incentive framework (e.g., payer or regulatory policy changes) and market factors (e.g., competitor

developments). New predictions of economic viability are considered alongside the clinical data generated in each trial phase, and any moral considerations, to yield Go/No-Go decisions.

How doesthis model work in rare diseases?

Historically, not well. Though on balance cost, time and risk of orphan development might be slightly more favourable than for non-orphans[1], this is not enough to compensate for the limited commercial opportunity afforded by rare diseases. Patient numbers in rare diseases are sometimes hundreds or thousands of times lower than in common conditions, with significant uncertainty about the real prevalence and the ability to reach patients. The limited revenue potential makes for a poor economic case given the standard pharmaceutical incentive frameworks and market dynamics. Consequently, very few medicines were being developed for rare diseases before the introduction of orphan legislation in the US (1983) and EU (2000).

Since the late 1990's, two crucial changes to incentive frameworks have improved the economic rationale for orphan development: legislative incentives and prices. The calibration of incentives spearheaded a wave of investment. The US and EU legislations enacted the provision of marketing exclusivity, a form of IP which protects not just against the entry of generics or biosimilar, but also against that of similar molecules without added benefits for the patient. This incentive has proved particularly important for some products (such as repurposed medicines), that would otherwise have no IP.

As important as market protection is price. Put simply, for the economic incentive to be similar to that of a treatment for a common disease, the price has to be proportionally higher (presuming all other factors are the same, which they might not be). Orphan medicine price levels did not directly ensue from the orphan regulation, nor are they a consequence of the monopoly granted by marketing exclusivity (as some suggest). Rather, payers, partaking in policymakers and regulators' sentiment of urgency, came to be willing to accept significantly higher prices than for comparable non-orphan products. This change has been a central driver of the observed innovation boom. Investment today remains deeply sensitive to payers' willingness-to-pay.

2. Are orphan prices too high?

Those prices are now the source of great controversy. How do you determine what a fair orphan price should be?

EU prices are value-based

For the last 20 years, there has been a growing consensus between manufacturers and payers that prices should be based on value. In countries like the UK, which use cost-

[1] Orphans have a slight (and uncertain) advantage on non-orphans in terms of development costs and time: although development requires fewer and smaller trials than non-orphan one, additional pre-clinical research is needed and trials are more difficult to conduct (e.g., recruitment challenges, numerous sites). Similarly, in aggregate chances of approval for orphans are likely higher than for non-orphans: drivers of increased risk (lack of disease knowledge, novel endpoints, unproven surrogates and highly heterogeneous patient populations) are balanced by the higher willingness of regulators to approve orphan products on the basis of sometimes very limited evidence. The literature contains contrasting reports on these topics, and any difference is likely to be marginal.

effectiveness to inform reimbursement decisions, the relationship between an acceptable price and value is made explicit: a maximum of £30,000 per quality-adjusted life-year (QALY) for most medicines. In other countries, like Germany and France, where pricing negotiations are not based on cost-effectiveness, price potential is still clearly linked to the perceived added value of the medicine, as measured by 'ASMR' or 'Added Benefit' ratings.

If you take a utilitarian approach, which holds that the value of a unit of health gain is the same regardless of the disease, orphan prices are hard to justify. This is why less than half of orphan medicines receive positive recommendations in the Single Technology Appraisal (STA) pathway at NICE, where the incremental cost-effectiveness ratio (ICER) threshold applied is the same as for any other disease (Zamora, et al., 2019).

Orphan medicines cannot be economically sustainable at the prices implied by such a low cost-effectiveness threshold. As discussed in the previous section, small populations make investment impossible if prices are aligned with those of medicines for more common diseases. Payers understand this, but face two important questions:

a) How much is society willing to pay for orphan medicines?
b) How much does society need to pay to incentivise orphan development while avoiding over-paying?

Society's willingness to favour rare diseases is ambiguous

The first question has attracted growing academic attention, eliciting multiple surveys of societal preferences for funding rare disease medicines. The findings are somewhat complex (and nuanced by methodological challenges), but collectively the literature, summarised by Drummond and Towse (2014), suggests three slightly contradictory things:

- People want health investment to target areas of high unmet need
- They do not value rarity *per se*
- However, they do think that everyone should have fair and equal access to healthcare (for example, they appear inclined to give priority to the treatment of ultra-rare diseases).

Despite the apparent lack of consensus for giving rare diseases special treatment, payers have demonstrated a higher willingness-to-pay for orphan medicines than for treatments for common conditions. In some countries this is overt: the UK highly specialised technology programme has an ICER threshold up to 10 times higher than the STA pathway threshold. A recent study found a significant inverse correlation between annual treatment costs and rarity in all EU countries analysed, with the correlation proving stronger as rarity increased (Medic, et al., 2017).

How can we determine optimal prices for orphan medicines?

Payers mostly accept that higher prices are necessary for rare disease medicines to be economically viable. At the same time, they have been asking – not unreasonably – *how much* higher orphan prices need to be. This is a question that the industry has not been very good at answering.

To many payers, policymakers, and patient associations, the answer to that question lies in the economics of drug discovery and manufacturing. Two recent examples of this are the pricing approaches proposed by the International Association of Mutual Benefit Societies (AIM) and EURORDIS (AIM, 2019; EURORDIS, 2018). Both approaches seek to establish 'fair' prices by incorporating R&D and commercialisation costs of the product in question.

These proposals draw a strong reaction from the industry, which sees them as ‘cost-plus’ pricing – the antithesis of value-based pricing. But they cannot be dismissed lightly, and the fact that industry has relied on business economics arguments to justify higher prices (i.e., orphan medicines are otherwise economically unviable) means that both sides are sharing a common logic. While I see a rationale for considering business economics elements in orphan pricing, the proposals from AIM and EURORDIS share some technical shortcomings.

Firstly, if stakeholders want to understand the price at which an orphan medicine is an economically viable investment (let’s call it the ‘innovation price’), they must consider both the risk of development and the opportunity cost of capital (i.e., discounting). Cost-plus methods don’t work for drugs because they usually omit to consider the very high rate of trial failure and very long development time. Hence, they greatly underestimate the innovation price.

Secondly, accurately assessing the innovation price requires correctly quantifying factors that are exceedingly difficult to estimate, especially in rare diseases. Perhaps the most important unknown variable is the number of patients who will ultimately receive the treatment. The prevalence recorded by the EMA tends to be higher (often by an order of magnitude) than the number of patients eventually treated. Challenges in diagnosis, prescription, access, and compliance can reduce the actual patient population. This gap probably helps to explain why AIM estimates that a ‘fair’ annual price would lie around €20-25K for orphan medicines and €30k for ultra-orphan ones, numbers that would almost certainly prevent the introduction of such medicines in Europe were they mandated.

Thirdly, attributing the R&D and commercialisation costs of a whole company to a single product is an extremely difficult accounting task, especially for companies that have multiple products in their portfolio. Furthermore, as with all accounting, there would likely be subjectivity in how costs are attributed, with companies highly incentivised to inflate development and manufacturing costs. There is no realistic prospect that payers could audit such numbers.

For all these reasons, undertaking product-specific cost-plus pricing is unlikely to be either feasible or effective. Nevertheless, if an answer to the question ‘how much is enough?’ is to be found, innovation economics must play a part in orphan pricing. But, crucially, this should be at the payer framework level, not at the individual product level. This was the insight that Mike Drummond and Adrian Towse outlined in an important paper (Drummond & Towse, 2014) and which, together with Mikel Berdud, they advanced in a subsequent study (Berdud, et al., 2020).

In the analysis, they framed the question slightly differently: at what price level are incentives to develop orphan medicines aligned with incentives to develop non-orphan medicines? This is a good way to formulate the problem if the objective of policymakers is to equally encourage drug development, irrespective of prevalence. They undertook the analysis from the perspective of the UK healthcare system and accounted for the different cost and risk of orphan vs. non-orphan development. Their findings, which I’m sure they would agree are only indicative, suggested that ICER thresholds would need to increase proportionally to the decrease in population size, such that extremely rare diseases (those affecting less than 1 in 50,000 people) would require a cost per QALY of £937K to equalise investment incentives with non-rare diseases.

Payers will undoubtedly shudder at this notion, and no one is proposing that thresholds introduced by Berdud *et al.* should be transposed directly into payer systems. Yet this work provides an indication of what the innovation price might be for orphan medicines.

Accordingly, it should be considered by payers when refining their assessment frameworks, alongside other factors, such as societal preferences. By doing so, payers could create value-based pricing frameworks that simultaneously anchor orphan drug prices to innovation fundamentals. To me, it is crucial that all stakeholders collectively engage in this reflection, so that no one believes that prices are arbitrary and unfair.

3. Are patient access and the reduction in unmet need adequate?

Access in EU is routinely limited and delayed

Perhaps the biggest complaint against the advance of orphan medicines in Europe over the last 20 years is that an insufficient number of affected patients have received access to this innovation. EFPIA Patient W.A.I.T. data suggest that, on average across Europe, approximately half of the orphan medicines approved between 2015-2018 are available[2] for patients (EFPIA, 2020). The degree of availability appears correlated with country income: wealthy European countries such as Germany (51 medicines available of 54 approved), Denmark (43/51), and France (41/51) have relatively high availability, while lower-income countries such as Latvia (0/51), Lithuania (2/51), and Poland (7/51) have very low availability. It should be noted that the correlation between income and availability is far from perfect, reflecting the multifactorial nature of access constraints, as will be discussed below.

The delay between marketing authorisation and reimbursement of orphan medicines can also be very long, reflecting the complexities (and sometimes inefficiencies) of P&R processes. W.A.I.T. data show that the time between authorisation and reimbursement for orphans varies between 111 days on average in Germany, to 618 days in France and 1,138 days in Poland.

Even when medicines are reimbursed, it does not mean that all patients who might benefit from them – as defined by the label – are receiving them. Reimbursement is often constrained to a sub-population. In France, nearly half of 'available' orphan medicines are restricted within the label, as are a substantial proportion of orphans in the UK, Sweden, Switzerland, and Portugal.

The outcome of reimbursement negotiations is probably the single biggest barrier to patient access for orphan medicines, but it is not the only one. One factor that comes before reimbursement negotiations is the decision by a manufacturer to seek reimbursement. In many of the countries where access is lowest, manufacturers may not have sought reimbursement for various reasons (discussed below). Other barriers exist beyond national reimbursement. In some countries where funding is held at the regional level, such as Spain and Italy, national price negotiations do not necessarily mandate local coverage, resulting in disparities of access between regions.

What are the underlying factors behind this lack of availability and delays? I see three main issues, related to a) pricing and funding, b) country infrastructure, and c) manufacturer capabilities.

[2] "*Measured by the number of medicines available to patients in European countries. For most countries this is the point at which the product gains access to the reimbursement list*"

Pricing and funding issues make reimbursement negotiations fail

Reimbursement negotiations fail (or companies don't launch because they expect them to fail) because of a mismatch between the price at which payers are willing to buy and the price at which companies are willing to sell.

In negotiations of such importance, it is tempting to view it through a Manichean lens: rapacious pharma companies vs. heartless payers. The reality is that on both sides of the negotiating table are good people, trying their best to help patients within the institutional constraints imposed by their organisation and the wider legal and regulatory frameworks. Therefore, I believe that a more dispassionate examination of institutional interests goes further in explaining lack of availability and delays.

Let's start with manufacturers: what are their constraints in reimbursement negotiations? Primarily, these relate to issues of return on investment. At the very minimum, a product must be profitable at country level (that is, the price must exceed the cost of manufacturing and distribution). But at global level, the collective revenue from international markets must not only be sufficient to cover marginal costs, but also be economically viable in terms of innovation. In other words, the total global return from a product must be sufficient to have justified the original investment in its development, and thus be enough to make future drug investment sustainable too.

It is therefore the total global revenue that is of ultimate importance when manufacturers consider the economic sustainability of the price of their medicines. In theory, were individual country negotiations completely independent, companies would sell at any price above the marginal cost of production and distribution. However, that is far from the reality of global drug pricing. The existence of international reference pricing (IRP) schemes, whereby countries formally or informally link their own prices to those in other countries, is probably the most significant obstacle to patient access in lower-income countries, and part of the reason why companies stagger launches across geographies. Financially, the risk of large price reductions in major markets outweighs the potential additional revenue from launching at lower prices in smaller markets.

This risk has increased considerably since the US began to express an interest in referencing EU markets. It has proposed an International Price Index that would link the prices of Medicare Part B drugs to those in a basket of other countries, including ones with income levels substantially lower than the US. Whether or not the proposal gets implemented in its current form, it already influences corporate decision-making, reducing companies' willingness to be flexible on non-US prices for fear of potential implications for US revenue. Should things progress on this front, patient access to orphan medicines outside the US will be impaired by the need to maintain a tight price band with the US.

Payers also face constraints in reimbursement negotiations, which can broadly be categorised as willingness-to-pay and ability-to-pay. The latter is ultimately a function of the wealth of a country and the extent to which it prioritises investment in medicines (drug spend as a share of GDP). Payers usually set a budget on an annual basis and have little potential for exceeding it. The drug budget sits within a wider healthcare budget, but opportunities to move money from other healthcare budget items are limited. Money for new medicines, unless previously budgeted, must be taken from savings elsewhere. In practice, this means that payers often have a relatively fixed amount of money available for any new drug.

Willingness-to-pay is a more complex (and controversial) consideration. This refers to the explicit or implicit thresholds that payers have determined to limit the price of medicines

according to their perceived value. In countries that use cost-effectiveness, such as Sweden and the UK, thresholds are explicit. In other countries, they are based on informal benchmarking between disease areas. Payers in both types of market are concerned that exceeding these thresholds for one drug will set a precedent for all others, causing general inflation of drug prices.

Unsurprisingly, there is interplay between willingness and ability-to-pay. Sovaldi in hepatitis C is the classic case of a value-based price that translated into a budget impact that exceeded payers' ability-to-pay. A country's willingness-to-pay may also be misaligned with its ability-to-pay, as determined by its income level. For example, the gap between Norway and Greece' willingness-to-pay is lower than would be expected given their respective GDP level.

All this makes it harder for companies to create coherent price structures across geographies that differentiate by ability-to-pay (and hence offer best chance of optimal patient access). While countries keep referencing prices to other countries and having divergent levels of willingness-to-pay, differential pricing will continue to be imperfect and untransparent.

Issues related to country infrastructure and manufacturer capability thwart patient access

Beyond pricing and funding, patient access to orphan medicines can be affected by the level of healthcare infrastructure in their country. Perhaps most importantly, diagnosis is a major impediment to access in rare diseases, particularly for diseases for which no treatment was previously available. The lack of specialist treatment centres, and patients' inability to be referred and travel to them, is also an impediment in many countries. For cell and gene therapies to be provided, specialist centres must have sophisticated genetic capabilities and capacity for related care (such as ICU beds), which are often unavailable.

Manufacturer size and capabilities also affect the speed and breadth of medicine availability and accessibility. Large companies with affiliates in most countries are likely to have sufficient local technical expertise to navigate payer processes across Europe (e.g., know- how to submit HTA dossiers). For example, Biogen has launched Spinraza in 29 European countries as of 2020 (SMA Europe, 2020). When large companies do not submit for reimbursement, it is most likely because of an expectation that they will not be successful (due to pricing constraints discussed above) or a consequence of a launch sequencing strategy. Smaller companies, however, may lack the internal capacity and local expertise to launch in small countries in which they have no presence. (The use of distributors still requires considerable oversight and can come with compliance risks.)

Addressing unmet need requires correctly identifying where need is

While patient access to approved medicines is the most obvious opportunity for improving rare disease patient treatment, a related concern pertains to the direction in which research and innovation is focused. Rare diseases stakeholders, in particularly the European Commission, worry that orphan drug research is happening in too few diseases and that many pipeline orphans (82% in 2016) are being developed for indications in which an orphan drug is already approved (Technopolis Group, 2020). While this concern is understandable, it does not fully reflect the process by which innovation happens and how patient outcomes improve over time. It also fails to recognise that rare disease burden is not equally distributed across diseases.

Unmet need in rare diseases can be (simplistically) quantified as the total number of rare disease patients multiplied by the gap between their health states and that of the general population (the "normal" quantity and quality of life). Wakap *et al.* (2020) have shown that about 80% of the population burden of rare diseases is attributable to 149 diseases. It's not surprising, nor unhelpful, that most of the orphans developed to date have targeted these diseases.

Most remaining unmet need still sits in these diseases. One licensed orphan drug does not equate to the alleviation of all unmet need. It is exceptional for the first wave of innovation to alleviate the vast majority of the disease burden (imatinib in CML could be an example). Instead, innovation happens incrementally over multiple products. Haemophilia is a good case study: unmet need has been reduced over 50 years through gradual improvements in medicines and treatment protocols, allowing haemophilia patients' life expectancy in rich countries today to be comparable to that of the general population.

By contrast, outcomes are still poor in Duchenne Muscular Dystrophy (DMD), which has seen very few medical innovations over the same period. Licensed orphans have since become available, but it is clear that additional innovation is required to reduce unmet need to a similar extent as haemophilia.

Any debate about adjusting incentives according to unmet need must start from a correct assessment of burden. This could take the form of an analysis of the Disease Adjusted Life Years lost per rare disease, like the one undertaken by the World Health Organisation for more common disorders. As far as I am aware, no one has done that assessment, even crudely. It would surely be a tough exercise, yet without such an assessment, any policy that seeks to target innovation at unmet need risks badly misjudging the situation and mis-calibrating incentives.

It might well be altogether unnecessary for politicians to adjust the orphan regulation to ensure unmet need is addressed. Payer systems inherently incentivise research in areas of high unmet need, for the most part. Manufacturers know that treatments aimed at high- burden diseases carry a higher value, better price, and quicker uptake.

Nevertheless, payer systems confound this incentive by benchmarking the price of a novel entrant to that of the standard of care *within the disease*. Companies are essentially incentivised to develop medicines for diseases with an existing high-priced standard of care, and disincentivised from investing in underserved conditions managed with low-cost, sometimes off-label (if referenced in clinical guidelines), treatments.

As an aside, it seems ironic that one of the medicines that is most often used off-label in rare diseases – rituximab – was once considered an unaffordable treatment with an excessive number of indications. Now, it is the go-to low-cost.

What about ultra-orphan drugs?

Ultra-orphan diseases are those that affect less than 1 in 100,000 people. Nearly 85% of the 5,100+ rare diseases defined by point prevalence on Orphanet touch less than 1 in 1,000,000 people (Wakap, et al., 2020). Given their extremely low prevalence, the economic hindrances to their development are exacerbated. Applying the same logic that the increase in price must be commensurate to the decrease in prevalence to make development economically viable, the price point required for extremely rare conditions is increasingly unattainable in Europe.

Yet industry's more limited interest for the rarest conditions does not only arise because of unfavourable economics. It is also somewhat of a 'low hanging fruit' strategy to address most unmet need. Let me explain. According to Wakap *et al.* (2020) "*77.3–80.7% of the population burden of rare diseases is attributable to the 4.2% (n = 149) diseases in the most common prevalence range (1–5 per 10 000)*". It seems that focusing on just a sliver of the 7,000-8,000 rare diseases identifies stands to deliver large benefits to a majority of patients.

That is of course not to ignore the plight of the remaining fifth of patients suffering from the rarest diseases. For innovation to happen in the long tail of very rare conditions, it is probable that a completely different business model is warranted, as the traditional biopharmaceutical regulatory requirements will always make investment impossible.

4. Are orphans over-incentivised and excessively profitable?

The perception that orphans are over-incentivised and excessively profitable is one of the main complaints behind the European Commission's decision to re-open the orphan regulation. That approximately half of all drugs in development are now targeted at rare diseases is taken by policymakers as proof that orphan policies are unnecessarily generous. This has been reinforced by the commercial success of some orphans, which have achieved global sales in excess of $1bn. The fact that the space is increasingly dominated by large companies, whose businesses appear to policymakers to be highly profitable, further engenders scepticism.

Analyses show that the EU environment is not unduly generous for orphans

Against this backdrop, we conducted a study to assess whether European incentives for orphan drug development are balanced. We used a rNPV approach, such as that described above (Neez, et al., 2020). This methodology allowed us to analytically mirror how companies make investment decisions, given the incentive frameworks and market factors in place.

Our analysis suggested that, even with the incentives currently afforded by the EU orphan legislation, the economic case for orphans remains marginal. That is not to say that the legislation hasn't been widely effective: our analysis also showed that the legislation was responsible for half of the orphan innovation seen in the last two decades. In short, the legislation increased the economic case for the average orphan drug from insufficient to adequate.

In our analysis the change in business case for orphans followed from the provision of regulatory incentives in the legislation (mainly, 10-year marketing exclusivity), but also from companion legislation provided at the Member State level (e.g., recognition of 'unquantifiable benefit' in the German AMNOG process, exemption from clawbacks in Italy, lower rebates in Spain).

This speaks to an important recognition of the role of P&R systems within pharmaceutical development decisions. While the European Commission is now reviewing orphan legislation, following Member State concerns dating back to the Dutch Presidency in 2016, the orphan environment has already shifted. As I argued in a short paper in 2018 (Hutchings, 2018), payers have been tightening the P&R conditions for orphans in Europe since at least the financial crisis in 2008. They have curtailed development incentives by being less willing

to reimburse medicines with uncertainty, stricter in their assessment of value, and more frugal in their willingness-to-pay. For example, the share of orphan drugs receiving an ASMR I-III in France fell from 80% in 2007 to 16% in 2015.

Another signal that the EU environment for orphans is not unduly generous comes from analysis of revenue data. When estimating this in our model, using the best available data for orphan prices and prevalence, the predicted revenue was significantly higher than the observed IQVIA sales data reported by the Technopolis Group (average annual EU sales revenue of €50 million; Technopolis Group, 2020). The latter also aligned with sales data from an analysis of orphan expenditure we published in 2019 (Mestre-Ferrandiz, et al., 2019) and a review of reported revenue from companies' annual reports.

These data suggest that revenues from orphan medicines in Europe are significantly lower than what could reasonably be predicted at the time of the development investment. There is no way that revenues that low, when plugged into rNPV models such as ours, would yield positive investment decisions. Yet orphan medicines have indeed been launched in Europe.

The US largely uphold global investment and innovation

The most likely explanation for this difference is the impact of the US market. Our study focused only on Europe, to reflect the purview of the EU orphan legislation. Of course, pharmaceutical investment decisions are global: companies do not develop medicines for individual countries or regions. Our presumption in taking this approach was that Europe wants to be a hub for scientific research and contribute proportionally to global pharmaceutical innovation.

Is this a fair assumption? In situations where multiple countries benefit from a global good, there is always a risk of the 'free rider problem', where individual countries might not contribute sufficiently to maintain that global good. In this respect, industry commentators have drawn analogies with defence and global warming. The former, suggests that Europe has underfunded its defence capabilities due to the protection of NATO. The latter has shown Europe moving ahead of other regions to reduce greenhouse gases, despite the economic cost of that investment. Presuming the Technopolis sales data is correct, it appears that in the case of orphan drugs, the analogy is closer to defence.

There are several issues with Europe's dependency on the US. Firstly, it doesn't seem to align with Europe's ambition to be a global leader in science and innovation, and a responsible global citizen. Much as 190 countries have ratified the Paris agreement on climate change, all regions, and not least Europe, bear responsibility to contribute to medical improvement according to their means.

Secondly, even a small reduction in revenues could have a detrimental impact on patient access to orphans in Europe. Given the observed level of revenues, any shrinkage of incentives may make it no longer commercially feasible to launch in Europe.

Lastly, there is a significant risk that, should the US reduce its investment in medicines, global innovation will badly stall. Orphans are particularly susceptible to this. The risk is far from improbable given the bipartisan support in the US for proposals to introduce international reference pricing (IRP), amongst other cost-containment measures.

5. Is orphan spending affordable, efficient, and sustainable?

Assessing the affordability of orphan expenditure appears to be simple maths, and to yield a straightforward answer: multiply the number of orphan drugs, their prices, and the prevalent population, and you get… unsustainable expenditure. If you made it this far in the paper, you might suspect that the formula isn't so simple – and you would be right.

Orphan spending represents a small, if growing, share of total pharmaceutical expenditure

I recently revisited (with colleagues) predictions I made (with other colleagues) back in 2010 about the evolution of orphan spending in Europe. Back then, we forecasted that orphans would account for approximately 5% of total drug spend by 2020 (Schey, et al. 2011). In fact, according to the recent analysis we undertook on IQVIA data, orphans today account for closer to 8% of total drug spend across Western European countries (Mestre-Ferrandiz, et al., 2019).

At first glance, it might seem that orphan spending is growing much more rapidly than anticipated. In fact, the increasing share of orphan expenditure has less to do with faster orphan spend, and more to do with lower expenditure on all other medicines (i.e., the denominator in our analysis). We had predicted that the total pharmaceutical market would grow from 2010 to 2020 at its long-term historical average rate. In reality, the EU drug market grew very little in that timeframe, due in large part to austerity-induced cost-cutting post financial crisis. At the same time, many primary care blockbusters saw their patents expire (e.g., Lipitor, Plavix, Singulair, Zyprexa), resulting in large savings for health systems.

This picture of relative stagnation in total pharmaceutical expenditure in Europe was mirrored in another analysis I was involved in (Espin, et al., 2018). We sought to examine the historical and future pharmaceutical expenditure growth in Europe after adjusting for list-to-net differences. We found, based on historical data, that pharmaceutical spending averaged 2% annual growth between 2010-2016. We predicted that the same growth rate would fall to 1.5% between 2017-2021. While we will have to wait another year to check the validity of this latest attempt at future-gazing, the historical data (derived from IQVIA data) suggest that European payers have a firm grip of overall budgets. This seems reasonable: within Europe's public social security systems, payers enjoy a monopsony power that is a good match to industry's supposed monopoly power.

Considering absolute figures, orphan spending doesn't look unaffordable, either. IQVIA sales estimates show that orphan products generate on average €50 million in yearly EU revenue, with only 14% of orphans exceeding €100 million in annual turnover (Technopolis Group, 2020).

Collectively, these analyses suggest that over the last decade savings achieved from genericisation in high-prevalence conditions, which have benefit from sustained drug expenditure over multiple decades, have been redirected to fund specialised medicines, like orphans, within a mostly constant total drug budget.

Increased generic and (to a lower extent) biosimilar entry stand to enhance financial sustainability

What about in future? In our original forecast of orphan expenditure, we had assumed savings from generics and biosimilars. Actual spend was higher than predicted partly because no biosimilars have yet been introduced in the orphan space.

Nonetheless, there is clear potential for savings in rare diseases at the point of loss of IP, at least for small molecule medicines. Spending on imatinib dropped sharply when generics entered the market (it fell by nearly half within a year). Lenalidomide, the current highest selling orphan, will lose IP soon. Orphan biosimilars pose more challenges for a number or practical and economic reasons (Dowlat, 2016), but the development of a biosimilar for eculizumab by Amgen likely foreshadows the fate of the handful of other high-revenue orphan biologics. While the loss of such revenue is painful for individual companies at the time, it is critical that savings from older products be released after loss of IP, so that payers do not curtail expenditure by lowering the price or suppressing access to new orphan medicines.

Political sustainability is essential to continued orphan dynamism

From a purely financial perspective, it is therefore likely that European orphan expenditure is sustainable. A bigger issue is that of the efficiency of this spend or, put slightly differently, of the political sustainability of orphan expenditure.

We've discussed in a previous section that society's eagerness to pay more for rare diseases is not fully established. Even if the increase is orphan expenditure is well-managed, society may prefer to direct resources elsewhere. Perhaps more importantly, if patient access is continued to be seen to be constrained, the political will to fund orphans may dissipate.

Still, many arguments justify continued investment in rare diseases. Rare diseases have been ignored for decades, while investment and innovation have been focused on more prevalent diseases, thus delivering large improvements in outcomes. In many diseases, unmet need is lower, and the opportunity for further pharmacological improvement is smaller. Re-allocating funding from areas of relatively low unmet need to areas of higher unmet need makes sense and seems fair.

6. Conclusions and recommendations

So, where do we go from here? Below are a few high-level thoughts on areas for focus moving forward, based on my understanding of the situation.

1. Build trust around orphan pricing and the innovation model

From the work we have undertaken on this topic, I feel that the orphan innovation model is not inherently unfair and that it reflects the fundamental economic challenges of developing medicines in rare diseases. Which isn't to suggest that there are no examples of bad practice, nor that the innovation model and the wider policy framework can't be improved. But I do believe that the industry has nothing to fear from greater transparency on the economics of innovation in rare diseases.

Openness can help build trust. I see a need for more proactive engagement with all our stakeholders to build knowledge on the orphan innovation model and the role that price plays within it. Industry should also acknowledge the legitimacy of discussions of innovation economics when thinking about rare disease pricing. Furthermore, industry should work with policymakers and payers to ensure that P&R frameworks are correctly calibrated to incentivise orphan development. This would avoid going down the dead end of product level cost-plus pricing.

As we discovered when building our model of EU orphan incentives, there is currently a lack of adequate data on the critical components of the orphan innovation model (including cost of development and risk) and a lack of a robust understanding of the real-world treatable population for rare diseases. The industry has an interest in helping outsiders better understand these critical components of investment decisions.

2. Recognise that both volume and price matter

Patient access to orphan medicines in Europe is too low. As well as representing a needless unmet need for patients, it also diminishes the return that manufacturers obtain from their medicines. Expectations of low uptake, both across and within countries, increases the need for high prices, creating a viscous circle. If anything close to the potential treatable population in Europe received access, the magnitude of volume gain could allow for reduction in average prices. While the logic is straightforward, the solution is not. Perhaps the most important component is the barrier created by IRP rules and a lack of solidarity between countries on price (see next recommendation).

That is not the whole picture. Some companies are demonstrating that it is possible to routinely launch orphan medicines very widely in Europe. Yet, such widespread access is not standard. Risks of price contagion are sometimes exaggerated; companies can be overly conservative in managing this risk. As policymakers, companies must embrace the concept of solidarity and recognise that launches in some markets will be less profitable than in some others, while still contributing something to the return on investment.

More than any other issue, poor access is driving pressure for changes to orphan policy. While a perfect solution may not exist, everything must be done within existing constraints to improve access if we are to avoid further deteriorations to the policy environment.

3. Enhance European solidarity on price and access

The rollback of IRP systems, which have been growing steadily for two decades,isan essential prerequisite for greater price differentiation between countries of varyinglevelsof income. If countries wish to pay similar prices to their neighbours, it makes moresenseto collaborate on HTA and procurement between countries with similar characteristics,rather than linking prices to a large basket of geographically and economically disparatecountries.

However, more important than the technical rules of IRP systems is the politicalsentiment that underpins them. Here we have seen a consistent beggar-thy-neighbourattitudethat rejects the notion of common goods and the idea that countries should contributeaccording to their ability-to-pay. As I mentioned earlier, in other areas – such as climatechange–this mindset has been rejected in recognition of the greater good. There is thereforehopethat change can happen when it comes to the global benefits of biopharmaceuticalinnovation.

4. **Manage the US / EU price discordance**

While EU price solidarity is future ambition, US-EU price discordance is a major present risk to patient access in Europe. Comparing price levels between the US and Europe is tricky, not least because in both regions there are a wide range of prices at both the list and net level. Nevertheless, the perception of a significant price gap, even after accounting for income levels, is likely to reflect the reality. This is especially true for products at the later stage of their lifecycles, because prices increase over time in the US whereas they decrease in EU.

This gap is creating instability in the global biopharma innovation model, as the US market is increasingly underwriting the cost of investment towards new medicines, including orphans. While US citizens benefit from earlier access to new medicines and a more vibrant scientific sector, the political sustainability of this situation is increasingly fragile.

It has been suggested that this dynamic represents one of the biggest threats to patient access to new medicines in Europe. If US reference pricing leads to companies having to choose between the US market returns that underpinned their investment case and European access, it is likely the latter that will be impacted.

It is very hard to see a solution that is politically appetising on either side of the Atlantic. European health systems on average account for 10% of GDP expenditure. In the US, it is 18%. For pharmaceutical investment levels to be equalised, it will require an equivalent convergence of healthcare spend.

In the meantime, European patient access is going to become ever more reliant on confidential net price discounts – potentially as part of sophisticated outcomes-based agreements – that minimise the risk of negative reference pricing consequences.

5. **Design a new innovation model for ultra-orphan medicines**

The economics of orphan innovation are primarily a function of prevalence. Put simply, for innovation to be economically viable, higher prices must compensate for lower prevalence, everything else being equal. However, there is a limit to the price per patient that payers are willing to accept. The price per patient necessary to incentivise a development programme for the treatment of a disease with only a few hundred patients globally would be so high (multiple millions) that payers are very unlikely to reimburse it.

As Wakap *et al*. (2020) have shown, the majority of the 6,000+ rare diseases sit in this ultra-rare range of prevalence. It is very hard to see how medicines can ever be economically viable at acceptable price points under the standard model of development and approval. This issue is bigger than reforms to pricing practices or payer processes. It probably requires an entirely new model of drug development that dispenses with the normal requirements for multi-phase trial programmes per indication. A potential alternative might be to move to approvals of scientific platforms, accompanied by rolling data collection and evaluation of safety and efficacy. Such regulatory issues are well beyond my area of expertise, but from an economics perspective, it seems clear that this is the level of reform needed if that unmet need is to be met.

6. **Support the entry of orphan biosimilars**

The basic contract between the biopharmaceutical industry and society is simple: first industry gets rewarded for its innovations over the duration of patents, then society obtains

the benefits of those medicines at low prices in perpetuity. In the orphan space this deal is already working for small molecule medicines (e.g., imatinib), but not yet for large molecule ones. This does not result from any nefarious company behaviour. Rather, it reflects the difficulties of developing medicines in rare diseases and the relatively small commercial opportunity available. We can expect to see biosimilar competition at the point of loss of IP for the few biologic orphans that make large returns (e.g., eculizumab); for now, these are the exception rather than the rule.

This is a problem for the industry. If payers are unable to realise savings in older products and come to believe that the prices of orphan biologics will never come down, they will seek further savings at the time of launch. This skews incentives away from developing new medicines, which is clearly unwelcome.

It is therefore in all stakeholders' interest to work together to address the barriers to biosimilar development in rare diseases. The nature of these barriers has been described in careful detail (Dowlat, 2016); work is now needed to understand how these can be overcome. EURORDIS has in the past played an important role as a convener of stakeholders on topics of mutual interest – perhaps they could add this one to their list.

7. Improve the understanding of unmet need in rare diseases

The European Commission understandably wishes to calibrate the orphan regulation to encourage research that generates the most value to rare disease patients. However, current thinking on this topic seems to oversimplify the nature of unmet need and misunderstand the way that innovation incrementally reduces it. As a single medicine almost never fully alleviates a disease burden, defining only first-in-disease drugs as innovative (and thus worthy of incentives) is a mistake. It is likely that most of the aggregate disease burden exists in the 149 rare diseases that account for ~80% of all rare disease patients. Multiple waves of innovation will be necessary to meaningfully reduce burden in these diseases. Disincentivising follow-on medicines will prevent the Commission from meeting its goal.

An important first step to improve the quality of this debate would be to quantify the Disease Adjusted Life Years lost across rare diseases, as a way to inform policy and research priorities. It wouldn't be an easy task, but even a crude assessment would advance our very limited understanding of this situation presently.

8. Use appropriate comparators for price benchmarking

Price potential plays a critical role in determining the economic viability of orphan investments. In countries in which pricing is based on within-disease price benchmarking, the cost of existing standard of care becomes a critical factor in determining the price opportunity. This can create some significant distortions in the economic attractiveness of disease areas, particularly where old, off-label, low-cost medicines are used as price anchors.

In order to incentivise the developments of the most effective medicines, it is important that P&R systems are value-based and reflect the benefit generated by a new drug. However, in rare diseases the existence of very low-cost comparators threatens innovation in certain disease areas. There are valid reasons why within-disease price benchmarking is reasonable in general, but for orphans cross-disease comparisons of similar medicines should act as a complimentary benchmark.

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