White Paper

From Orphan to Opportunity: Mastering Rare Disease Launch Excellence

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Introduction

Medicines for rare diseases are a leading contributor to all novel drug approvals and launches. During the past five years, orphan medicines have typically represented more than half of new active substance approvals in the U.S., and on average 45% of approvals in Europe.[1] In fact, 143 drugs launched with orphan drug designation in the U.S. in the past five years, representing 53% of the 268 launches.[2] Clearly, rare diseases represent a significant focus of innovation with 44% of the clinical trial activity globally focused on rare diseases.[3] The high level of unmet need remains, with an estimated 95% of the over 7,000-10,000 rare diseases still not having treatments available.[4]

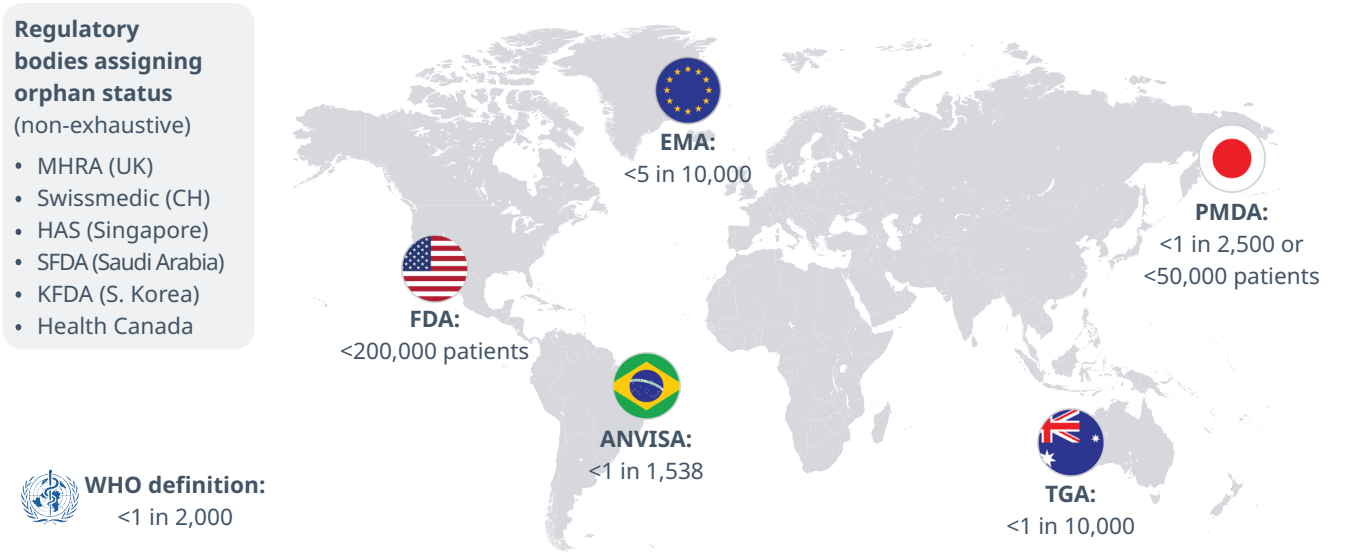
IQVIA's Launch Excellence series shows today's launch environment is tougher for innovative launches to fulfil their true potential in general,[5] and this is also the case in rare disease. Whilst legislation that introduced incentives for development in rare diseases (such as market exclusivities, financial waivers, and regulatory support) has been very successful at stimulating innovation in the rare disease space, with payers and policy makers recognising that some orphan 'exceptions' must change. In 2023, key policy changes/ proposals on both sides of the Atlantic ultimately threaten to make the environment more challenging for orphan medicines, as some of the key enablers for orphan drugs are changed or at risk.

With both biotech and large pharma heavily invested in rare diseases in their current portfolio and pipeline, and a challenging launch environment, it's increasingly important to learn every lesson from those companies, large and small, which play in the rare disease space and launches into rare diseases which have been successful.

First, define your terms

It's important to recognise that rare disease market definitions — of what a rare disease is, and what an orphan drug designation is — are not global or universal but defined within regions and by individual regulators (Figure 1). Definitions of a rare disease are population based, with upper limits on the number of sufferers per a given number of the population. The upper limits vary by country or region, and crucially, are defined against the population of that region, logical since an estimated 80% of rare diseases are of genetic origin[6] and therefore can vary significantly in prevalence across countries.

Figure 1. Orphan drug designations in selected countries/regions



Source: WHO; Rare Diseases International

The rules for orphan drug designation also vary by country. In the U.S., an orphan indication for a product with other indications that are not for rare diseases is currently allowed, so only a segment of the sales of that product are for rare disease. In the European Union on the other hand, the whole product is either orphan designated or not, and incremental approvals for non-rare diseases means relinquishing orphan status.

Within the envelope of rare diseases in each country/region, there's also significant variation — a higher prevalence rare disease, for example, Duchenne Muscular Dystrophy, which affects 1 in 3,500 male births within the U.S., is over 1,000-fold more common than the ultra-rare sialidosis, which affects 1 in 4,200,000 live births. Unsurprisingly, go-to-market models can also be very different within rare disease, dependent on prevalence of condition and other factors. Launching in rare disease requires flexibility and agility to adapt to different situations, and out-of-the-box thinking to address the truly novel nature of these treatments.

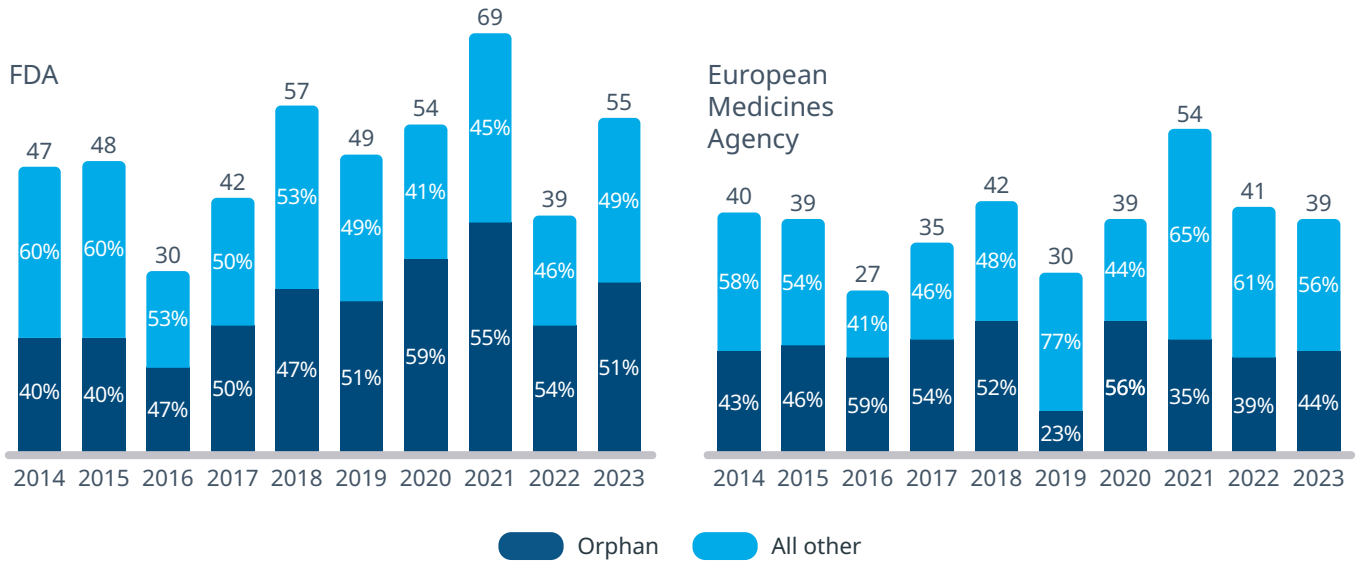
Defining commercial success for a rare disease product as a share of a global market is not meaningful — there is no single, global market for rare disease. Rare disease success requires different definitions of success which relate to the share of patients successfully treated for a given disease. We will explore how this plays out in practice. Rare disease medicines will have orphan drug designations, so could be referred to as orphan medicines, but as what orphan designation means in practice varies across the world, we will use both terms in this paper.

Rare disease markets: a legislative and innovative success

The success of orphan legislation in stimulating innovation in rare diseases is evident in the numbers: since the European orphan medicine legislation was introduced in 2000, almost 240 products with orphan status have been approved by the EMA, out of which 135 currently hold orphan designation status as of December 2023.[7] In the U.S., which passed the orphan Drugs Act earlier in 1983, that number is much higher, with more than 600 orphan products FDA-approved.[8] Orphan designation by regulators comes with incentives- in the U.S, with the FDA, these include tax credits for qualified clinical trials, exemption from user fees, and a potential seven years' market exclusivity after approval. In Europe, with the EMA, these include assistance on trial protocol, market exclusivity, and in some cases fee reductions. Once orphan medicines reach the European markets they have, historically, been able to benefit from a more forgiving HTA environment, and although in individual countries this may not always be the case, orphan medicines will be prioritised in the Joint Technology Assessment of harmonised European Health Technology Assessment currently being introduced. These incentives have had an effect: in recent years, orphan drug approvals typically make up more than half of new active substance approvals in the U.S., and on average 45% of approvals in Europe (Figure 2).

In parallel, rare diseases are becoming much more integral to company pipelines, portfolios, and structures over time. Total clinical trial activity peaked in 2021 and decreased in the following two years. Whilst large population disease trial starts decreased by 26% between 2021 and 2023, rare disease clinical trials were more resilient and only decreased by 17% in the same time period and expanded by 55% in the past ten years (Figure 3 left panel). This expansion was largely driven by emerging biopharma (EBP*) companies increasing their share of the rare disease clinical trial activity from 32% in 2013 to 61% in 2023.[9] Inversely, the share of large pharma-run clinical programs has decreased from 55% to 27% between 2013 and 2023. In the U.S., 29 drugs were launched with an orphan designation in 2023, and of these 14 (48%) were EBP launched,[3] and of the new active substance launches in the U.S. by EBPs in 2023, 51% were orphan medicines (Figure 4). In contrast one third of launches by large pharmaceutical companies in the U.S. in 2023 were orphans. Large pharma is also active in the rare disease clinical space, either organically with dedicated rare disease programs, or the inorganic acquisition of assets or entire companies, although large pharmaceutical companies are less focussed than EBPs on rare disease development and launch.

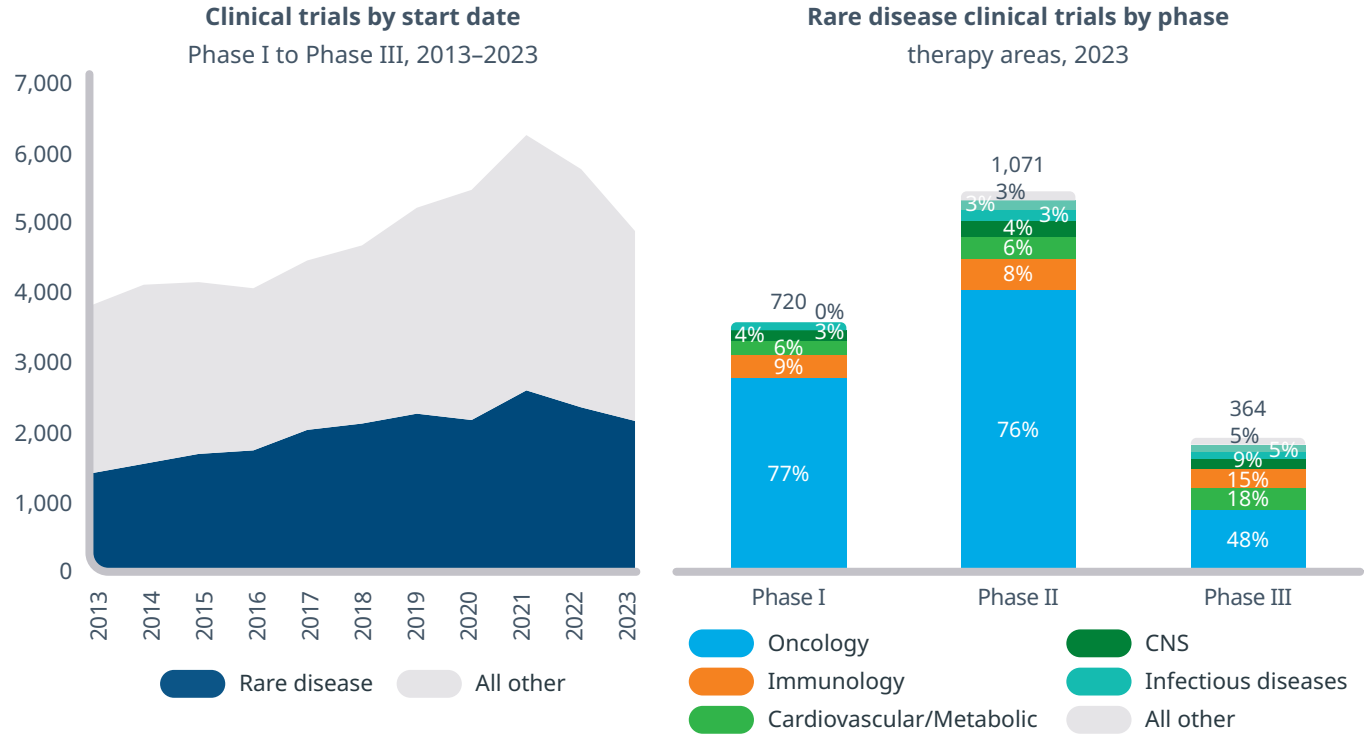
Figure 2. Orphan drug approvals



Source: EMA, FDA

*Emerging biopharma are companies with less than $500 million in global sales and less than $200 million in R&D spending per year.

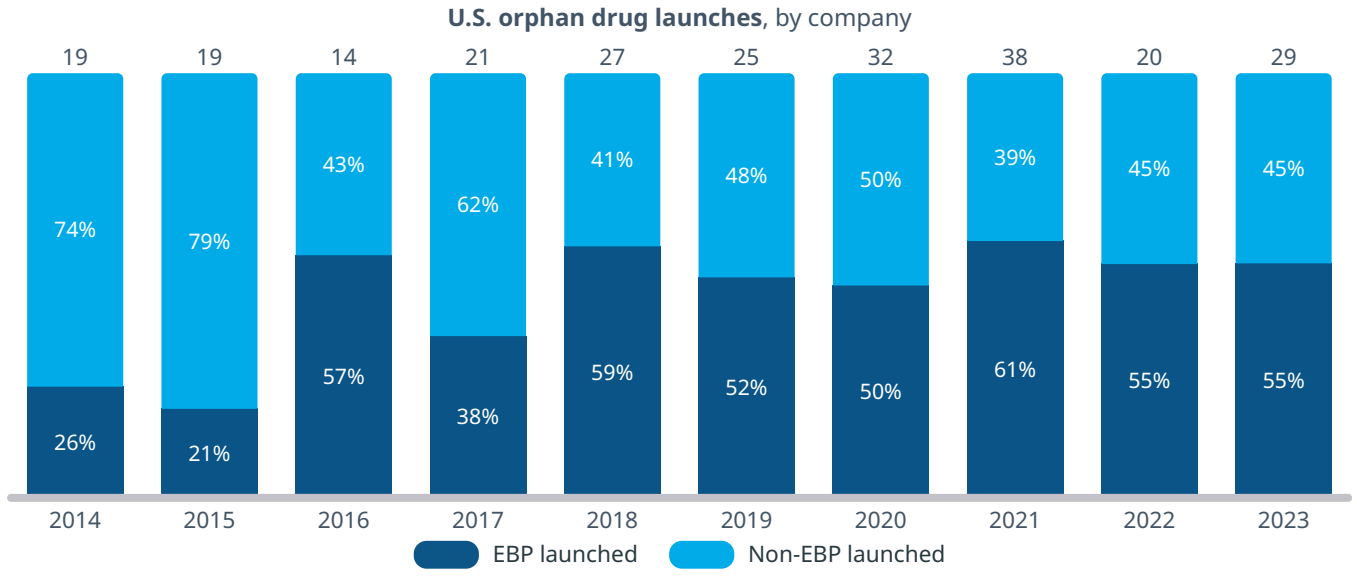
Figure 3. Rare disease clinical trial activity



Source: Citeline Trialtrove, Jan 2024; Global Trends in R&D: Overview through 2023; IQVIA EMEA Thought Leadership Analysis

Oncology is the largest therapy area within rare diseases accounting for 72% of clinical trial activity followed by immunology with 10%, cardiovascular/metabolic and CNS with 8% and 5% respectively (Figure 3 right panel). Oncology assets currently in late clinical development include next-generation biotherapeutics like CAR-T-cell therapies or mRNA cancer vaccines. Gene therapies for sickle cell disease or haemophilia saw pivotal approvals in the past few years. In haemophilia alone, over 15 phase III programs were launched in 2023. In CNS, treatments for amyotrophic lateral sclerosis (ALS), Duchenne muscular dystrophy (DMD) or myasthenia gravis are focus areas for the industry.

Figure 4. U.S. orphan drug launches



Source: IQVIA Institute

Post-pandemic launch environment for orphan medicines

Rare diseases are not for faint-hearted companies. The challenges of developing and launching products in rare diseases are extensive — small patient populations, limited disease understanding/awareness, limited evidence, and in some cases undefined regulatory pathways — to name only a few. However, they have been well-covered in prior reports, and therefore we will focus here on what has changed in the past few years, with a focus on go to market preparation and launch.

In our recent Launch Excellence white papers,[10] IQVIA has identified three major environmental challenges to the uptake and optimal use of all innovative prescription medicine launches, which were triggered, or exacerbated by the pandemic.[11] These are:

1. Lack of healthcare system capacity to adopt and optimally use new innovation, for example when, as is often the case for rare disease medicines, they are Advanced Therapy Medicinal Products (ATMPs) such as gene therapies

2. Increased challenge for pharmaceutical companies to have optimal engagement, with the right healthcare professionals, as with burnout and greater workloads, interaction opportunities have measurably decreased in many countries

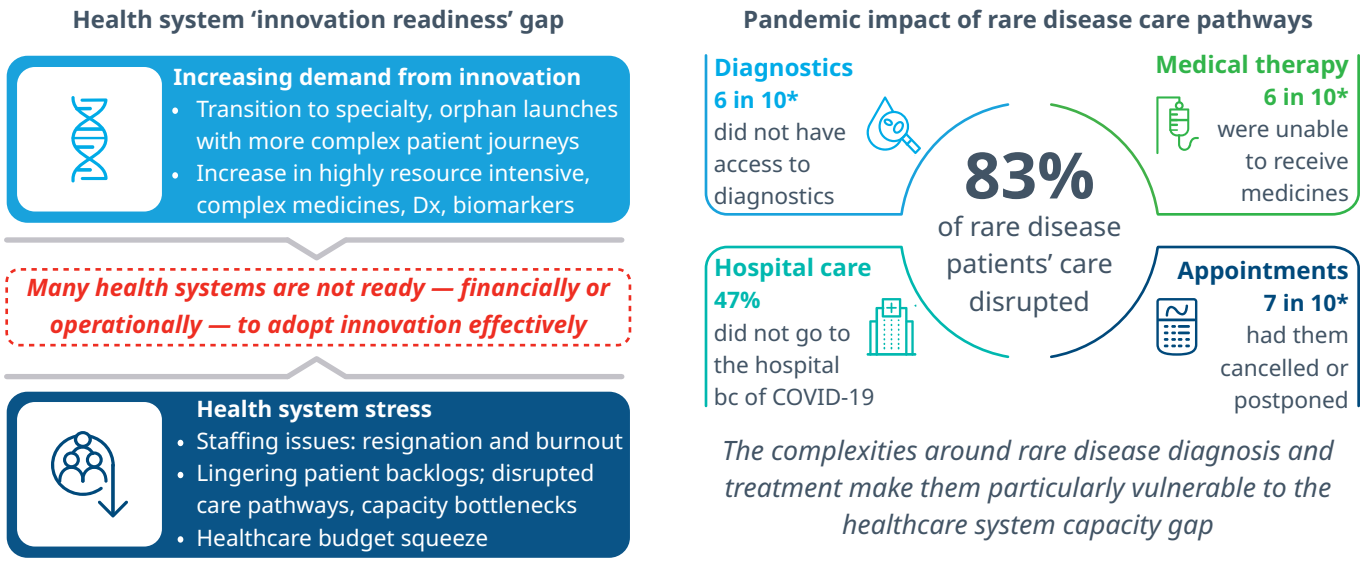
3. Negative impact of budgetary constraint across health systems, and in particular market access policies. Healthcare capacity gaps and market access constraints raise particular challenges for rare disease launches

These environmental challenges impact all launches, but they have special challenges for the introduction of rare disease launches.

A growing healthcare system capacity gap

More technologically sophisticated launches, which means most specialty products (including for rare diseases) and especially gene, cell and RNA therapies, demand more from the system at a time where healthcare systems are particularly strained in the aftermath of the pandemic (Figure 5). Diagnosis and treatment delays for rare diseases are common, one estimate being an average of 4 to 5 years for diagnosis, and with patients often seeing 7 or more types of specialists prior to receiving a correct diagnosis,[12,13] although the range in time is huge, since some rare diseases can be diagnosed at birth via screening, but others may only be diagnosed in adulthood. Delays in diagnosis and treatment can have catastrophic consequences for rare disease sufferers; a case in point is DMD a genetic, progressive condition which affects boys. While genetic screening can identify the disease at birth, studies show that in families with no prior history of DMD, delays between the onset of symptoms and a definitive clinical diagnosis were on average 2.5 years in the U.S., meaning boys were on average 5 years old by the time they received their diagnosis. In 2023, the FDA approved Elvidys, the first gene therapy for DMD, for patients aged between 4 and 5 years old. While it is possible that future approvals will extend this age range, the cut off means that boys experiencing diagnosis delays are unable to access and benefit from the treatment. Healthcare professional shortages, moves to remote care provision, and shortages in specialist diagnostic facilities are all health capacity gap challenges that can be especially challenging for a rare disease launch.

Figure 5. Health system innovation readiness gap and pandemic impact on rare disease care pathways



The complexities around rare disease diagnosis and treatment make them particularly vulnerable to the healthcare system capacity gap

*of those who experienced a disruption to care

Source: IQVIA EMEA Thought Leadership; EURORDIS Rare disease barometer survey, Nov. 2020

Rare disease launches are more likely than conventional launches to be highly resource intensive or require fundamentally new operations and resources — cell and gene therapies represent the extreme end of the spectrum, but all rare disease launches are likely to challenge health system capacity and existing ways of working in some way.

As an example, the hospital and healthcare system capacity required to deliver cell or gene therapies, (which are almost all to treat rare diseases) to a patient is considerable. A CAR-T cell centre administering a CAR-T orphan medicine such as Tecartus, (brexucabtagene autoleucel, a treatment for rare B Cell lymphomas) might need to address the following challenges:

- Purchasing apheresis machines, creating an apheresis unit, and stem cell lab freezing capabilities, ensuring Intensive Therapy Unit capacity is available
- Staffing up: apheresis nurses, CAR-T clinical nurse specialists, pharmacist, ITU consultant, data managers, CAR-T delivery coordinators, in addition to specialist doctors
- Training and accreditation of staff with the pharmaceutical companies providing the cell therapy, including training all staff which may interact with CAR-T patients in CAR-T cell toxicity such as cytokine release syndrome
- Creation and regular update of standard operating procedures, pathways and guidelines; i.e., hospitals become manufacturing sites — creating barriers to entry and limiting capacity
- Management of patients requires excellent coordination across all teams (hiring dedicated coordinators), including patient accommodation and accommodation for relatives and carers for extended periods

Gene therapies also necessitate dedicated staff with extensive training and carefully defined Standard Operating Procedures and coordination. Mandatory monitoring of patients who receive a gene therapy product over extended periods, between 5- and 15-years post administration, further increases pressure, and while costs of follow up fall on the companies behind the gene therapy, there are inevitable calls on the time of patients, most importantly, and their healthcare system providers.

Orphan medicines can, therefore, place considerable pressure on healthcare system capacity as while patient numbers are very low, the amount of capacity demanded per patient can be very considerable, and the growth in demand is forecast to be substantial. A 2023 survey of UK companies conducted by the Cell and Gene Therapy Catapult forecast a 63% growth in headcount in the UK

cell and gene therapy manufacturing sector between 2023 and 2028.[14] Whilst these document demand for specialist, skilled roles in the private sector, this growth would have to be mirrored by staffing growth in the UK's National Health Service and, given skills in these areas are in short supply, capacity tensions are inevitable. This trend will be mirrored across other countries.

A toughening market access environment

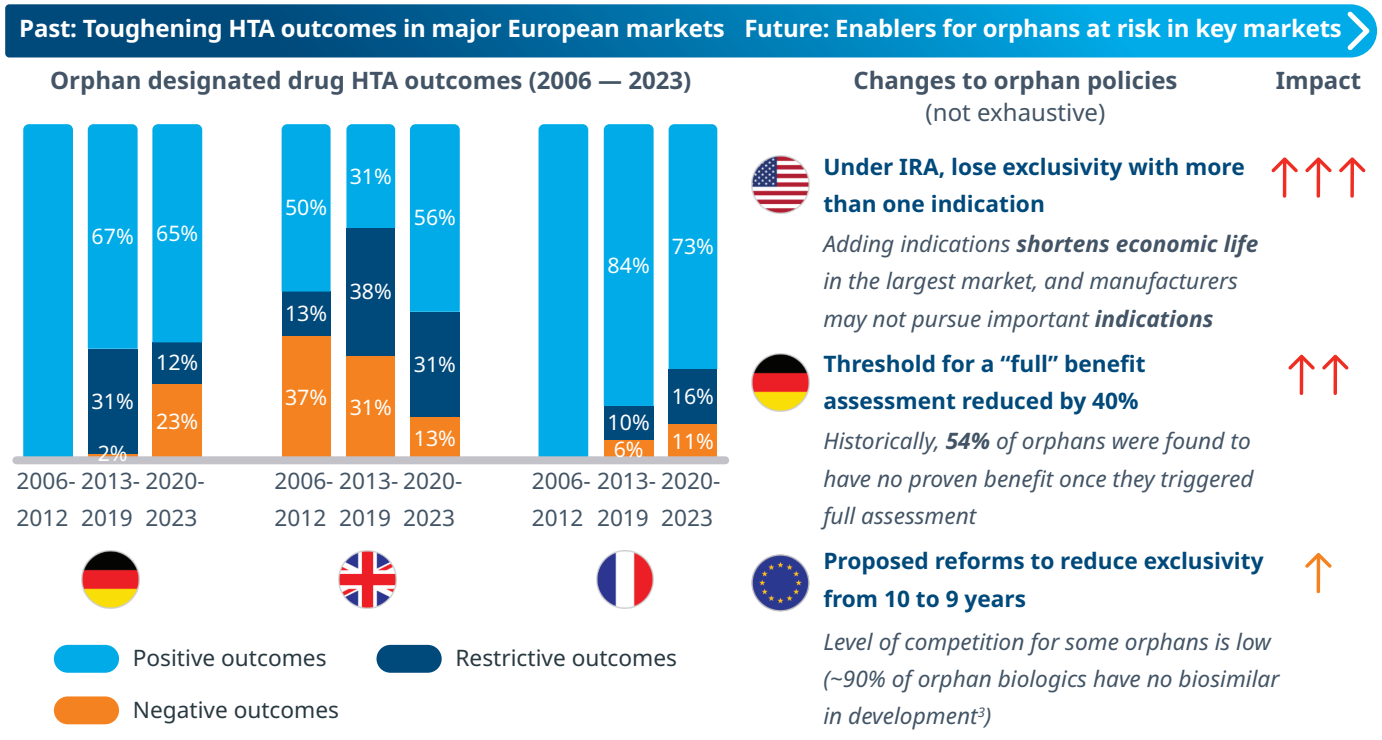
Rare disease products are often perceived as extremely high price, with headlines referencing million-dollar price tags per patient all too often a highly visible aspect of rare disease product launch. These headlines, of course, obscure the fact that the overall cost of rare disease treatments to medicines budgets is in fact quite small at 11% of total prescription spending in both the U.S. and Europe.[15,16] While per patient costs can be high, the number of patients is small, often exceptionally small for the highest cost treatments, which tend to be for ultra-rare diseases. Healthcare systems are not well set up to cover high upfront payments for curative one-off gene therapies costing $2 million or more per patient. Collectively, the volume of rare disease launch approvals in an environment where healthcare spending in general, and medicines budgets, are constrained, means that the rare disease market access environment is an increasingly prominent agenda item for payers and health technology assessors.

Cost-containment measures make the market access environment even more challenging.

Orphan medicines typically have limited/immature evidence packages and command high price tags, making them risky bets for payers. Moreover, specifically ATMPs are challenged by payers on the promise of their potentially curative nature where benefits are spread over years/decades whereas health system are looking at far shorter time horizons. A mixture of long-term trends (payer tightening of budgets), and new policies aimed at cost containment in the aftermath of the pandemic are making market access more challenging generally, and some policies go further to target orphan drugs (Figure 6).

In Germany, the GKV Stabilization Act, which went into effect in early 2023, reduced the annual revenue threshold that an orphan drug/medicine can generate whilst remaining protected from the full and rigorous HTA process from €50 million to €30 million. This means that orphan products will need to go through a full benefit assessment earlier in their lifecycle, which could be challenging, as historically 54% of orphans were

Figure 6. HTA outcomes and future policy changes affecting orphan drugs



Source: IQVIA HTA Accelerator; IQVIA EMEA Thought Leadership Analysis

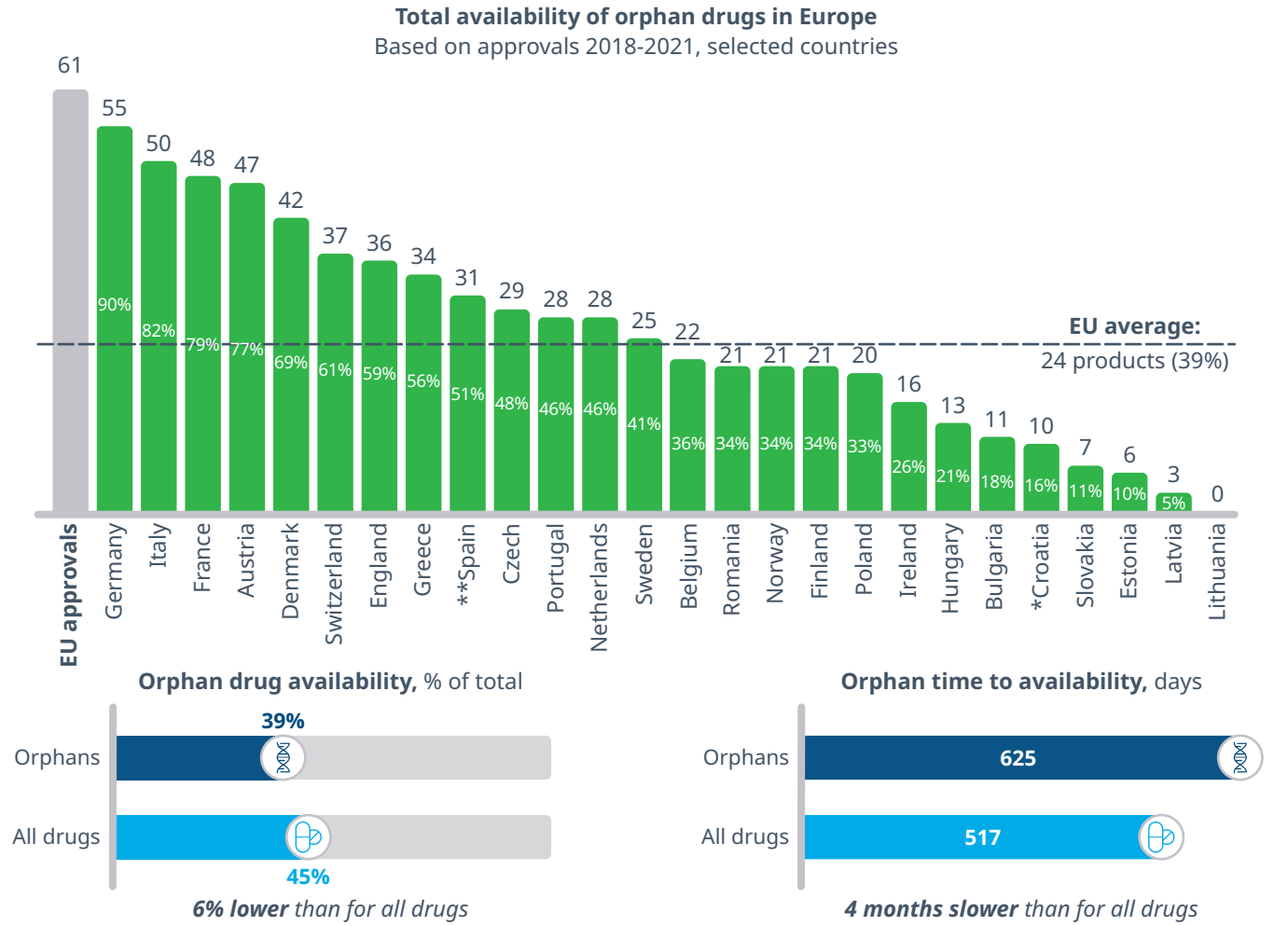
found to have no proven benefit once they triggered full assessment.[17] This policy change will likely have a high impact on the orphan medicine market in Germany, the largest European medicines market, with the best access to both innovative medicines in general, and orphan medicines in particular, according to the Patient W.A.I.T. indicator[18] developed by IQVIA in partnership with the European Federation of Pharmaceutical Industries and Associations (EFPIA) and local pharmaceutical industry associations.

Despite a single regulatory process and common approval date for orphan medicines in EU countries, rare disease patients are not getting equal access to orphan medicines, either seeing years of delay after approval for access or in some cases not getting access at all. An analysis of access for European countries within the EU and beyond shows that the availability of orphan medicines has historically varied dramatically — from none of the 61 orphan medicines approved by EMA between 2018-2021 in Lithuania, to 55 in Germany (Figure 7 upper panel). This disparity is sharpest for Central and Eastern European markets which have very little access to orphan medicines.

The average time to reimbursement for orphan medicines in the EU is 1.7 years and can range from as low as three months to as high as 2.5 years, which is far from the EU Commission's goal of improving access in all member states.

This access problem is further compounded for cell and gene therapies, with many not yet available in any market. This is in part due to the model employed by cell and gene therapy providers, where patients must be transported to a centralised centre for administration

Figure 7. Orphan drug availabilty in Europe



Source: EFPIA Patients W.A.I.T. Indicator 2022 Survey; European Union average: 24 products available (39%) †In most countries availability equates to granting of access to the reimbursement list, except in DK, FI, LU, NO, SE where some hospital products are not covered by the general reimbursement scheme. *Countries with asterisks did not complete a full dataset and therefore availability may be unrepresentative. **In Spain, the WAIT analysis does not identify those medicinal products being accessible earlier in conformity with Spain's Royal Decree 1015/2009 relating to Medicines in Special Situations

of the medicine; therefore, negating the need to have medicines made available in each country. Having said this, many research hospitals can carry out cell therapies using the hospital exemption in situations where access is lacking.

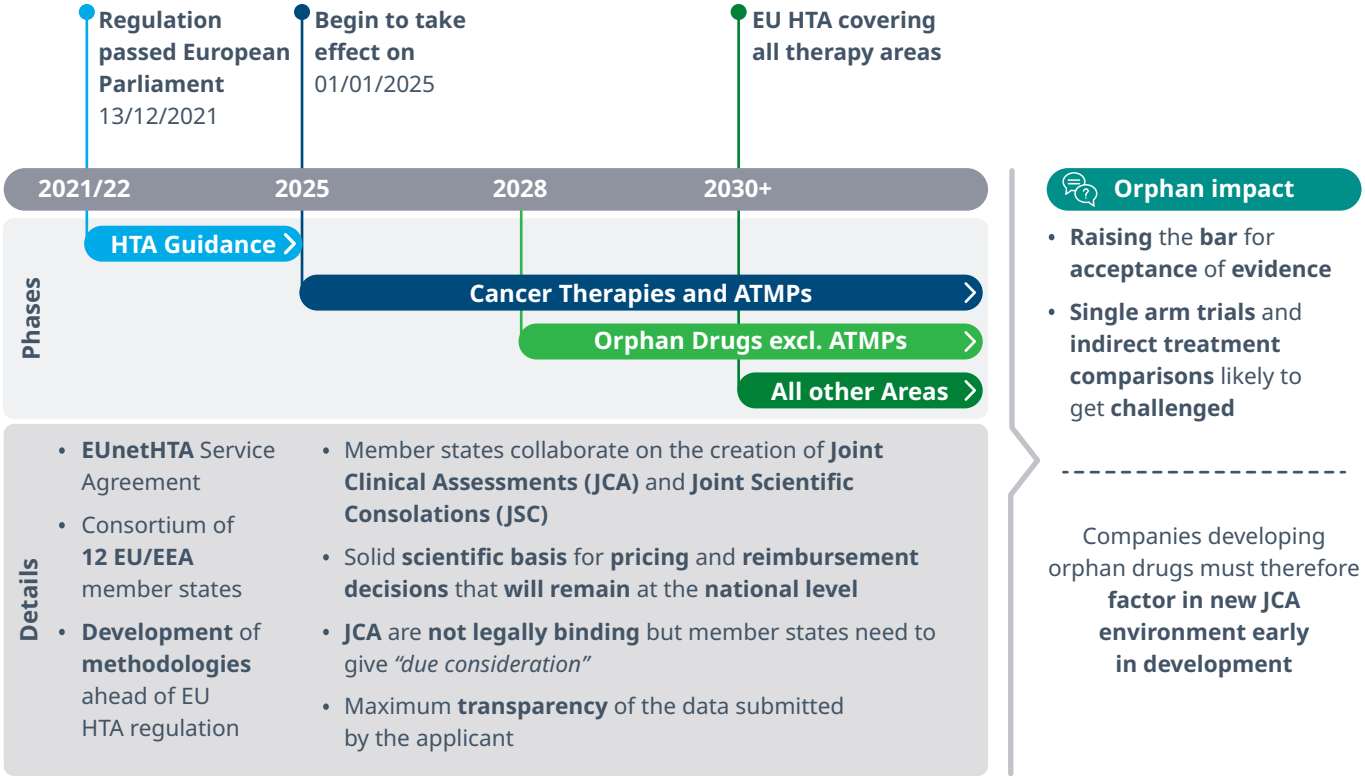
In 2023 the European Union proposed reforms to address this disparity in access by reducing orphan exclusivity from ten to nine years, but this can be extended to 13 years, up from 12 years today, as follows:

- 9 years orphan Market Exclusivity
- +1 year if medicines are launched in all EU member states
- +1 year if drug is a medicine of "high unmet medical need" (HUMN)
- +2 years on indication expansion (unchanged)

The additional year gained from launching in all EU27 member states is unlikely to be seen as a significant benefit to companies launching orphan medicines, which already struggle to launch across the EU.

Another pan-European Union initiative to harmonise Health Technology Assessment will impact orphan medicines in the EU earlier than most non-orphan medicines (Figure 8). The Joint Clinical Assessment (JCA) aims to replace parallel evaluations of clinical data by multiple country specific HTA bodies with a single harmonised relative effectiveness assessment. For orphan medicines that are ATMPs — for example gene or cell therapies, JCA is scheduled to start in 2025. For other orphan medicines, it will start in 2028. The underlying goal of this change is to harmonise assessment to improve access to orphan medicines based on their value to European patients; the practical impact may be to raise the bar for acceptance of evidence, with orphans presenting evidence from single arm trials (SATs) and indirect treatment comparisons (ITCs) more likely to see challenge. Companies developing orphan medicines in Europe must therefore factor in the new JCA environment as early as possible in development, paying particular attention to any differences in existing standards of care across Europe.

Figure 8. EU HTA and its orphan impact



EUnetHTA 21 consortium ended in September 2023 and the EU HTA coordination group and subgroups were set up, now awaiting the first of the four implementation acts to be put out for public consultation

Source: IQVIA EMEA Thought Leadership; IQVIA HTA Accelerator

In the U.S., orphan medicines with a single indication are protected from price negotiations under the Inflation Reduction Act, but they lose this exclusivity with additional indications, meaning that gaining additional indications may shorten their economic life. We expect this to have at least a medium impact, particularly since the U.S. is by far the largest and most important pharma market globally. It could also pose a risk that pharmaceutical companies do not pursue important indications and some groups of patients are left without treatment options which could benefit them.

Orphan medicines can lose exclusivity and see generic or biosimilar versions, and this should be a source of cost relief for healthcare systems, potentially freeing medicines budget for future innovation. However, evidence suggests that the off-patent market does not work effectively for many orphan medicines. In a study completed in 2023, Assessing the Biosimilar Void, IQVIA research found that only one orphan biologic so far has attracted biosimilar development, less than 3% of the entire cohort,[19] with lack of commercial return driven by small overall market opportunity and challenges in clinical development the most likely cause.

So what are the lessons learnt on how to succeed in rare?

Despite the environmental challenges we outline, there are plenty of reasons to remain optimistic about the orphan medicines market. Our previous research showed that immediately post-pandemic, orphan medicines were, on average, the most resilient group of medicines to pandemic disruption.[20] This is likely due to a combination of factors, such as continued high motivation within healthcare systems to treat patients with new treatments in areas where there is high unmet need, and in some cases, a pre-identified pool of patients waiting to benefit (for example, in diseases where screening programs exist or where patients have failed prior treatments).

How should we define success in rare diseases launch? Rare diseases have unique processes throughout development and commercialisation, with nuanced regulatory pathways, HTA processes and customer engagement models, and we must also

reflect their uniqueness in how we measure success. Many of the standard metrics used to measure commercial success, such as market share or sales are not the most relevant measures of success in rare diseases where there may be no competitors, small patient numbers, a highly varied epidemiology across countries, and often high levels of confidential rebates or pricing agreements.

On one level, we could define rare disease launch success as bringing to market any new treatment option for an underserved patient population. However, in this paper we will focus on how well a company executed on an orphan launch for both optimal patient impact *and* commercial success, building on the framework in our previous orphan medicines Launch Excellence,[21] where we argued that whether an orphan launch is Excellent or not is about how well it optimised on the following three areas:

1. **Clinical development effectiveness and label:** Poor trial design has, in the past, led to the failure of agents that in fact held significant promise for a rare disease. Promisingly, 2023 saw a trend break with composite clinical trial success rates for rare disease improving to 13.3% - a 5.7%-point increase year-over-year.[22] Clinical development of treatments for rare diseases is different to that for other conditions. Identification and recruitment of patients for trials can be a huge challenge if disease sufferers are inadequately diagnosed and frequently diagnosed too late for optimal intervention.[23] Trial designs can be a challenge; the optimal endpoints may not be clear, placebo control arms may not be possible at all or prohibitively slow and pose ethical questions. External comparators, also called synthetic control arms, are a solution but require real-world data on patients with the rare disease either to have been collected or to be collectable — again a challenge if identification of patients is low and slow. Orphan medicines can be granted conditional approvals which mean faster approvals but requirement for post authorisation studies and registries. Choices made in clinical development can have a critical effect on the uptake, impact, and commercial success of rare disease launches.

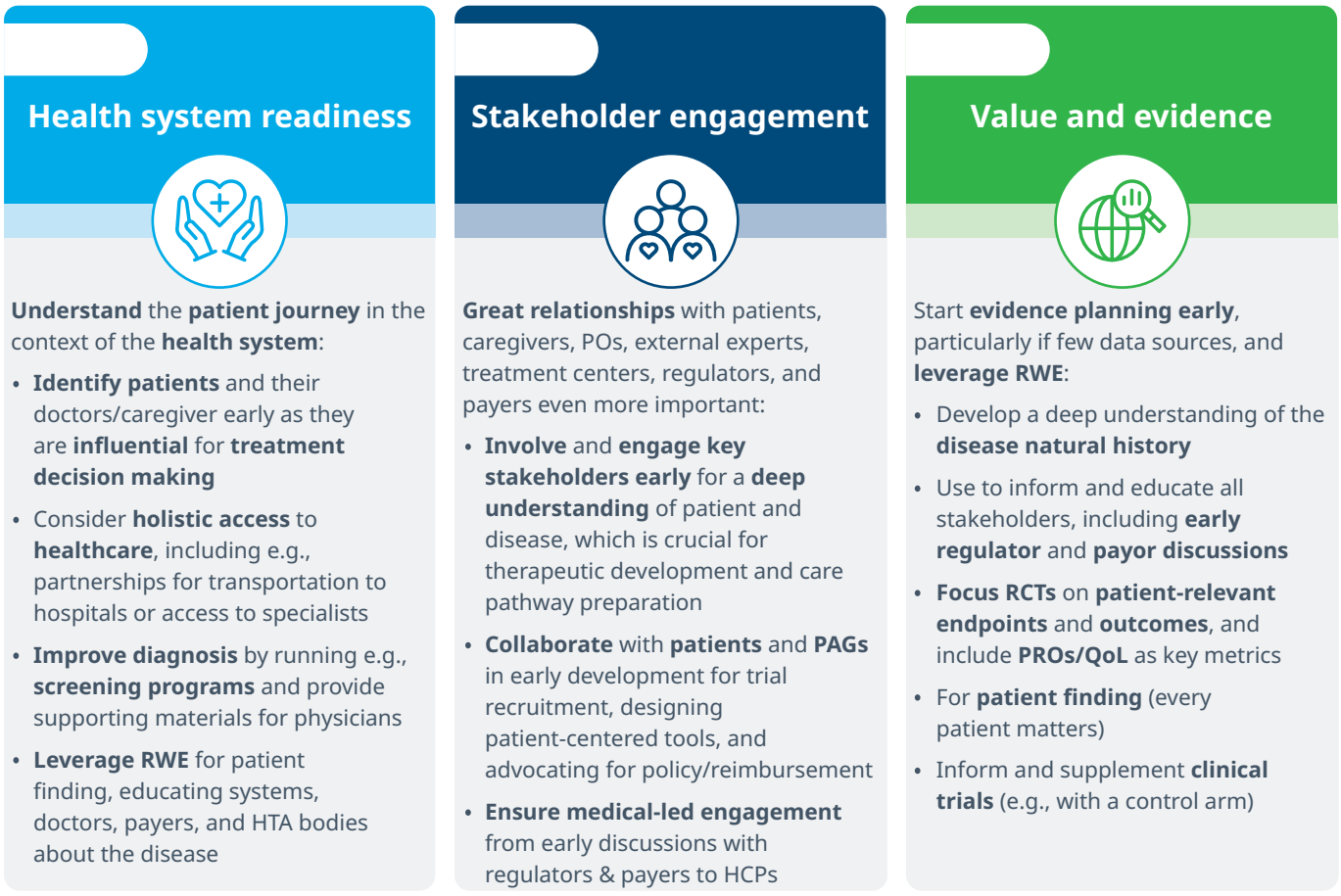
Choice of endpoints. Trial endpoints must be relevant for regulators, but also to payers and to the lived experience of patients. A critical challenge is balancing clinically measurable endpoints (which may often be surrogate markers) with increasingly important patient relevant endpoints. Patient centric endpoints are now either encouraged or required by regulators for all medicines in development — for example, as part of the 2016 21st Century Cures Act, the FDA allowed companies to provide "data summaries," real world evidence, and anecdotal data to support approval of new indications, including a required statement on patient experience data. However, for rare diseases, patient centric endpoints matter even more, because there will be few established, "off the shelf" endpoints to pursue, and to complement surrogate endpoints to provide a more holistic view of treatment value. An example occurred in the development of ruxolitinib (Jakafi) for high-risk myelofibrosis, a condition causing the enlargement of the spleen or liver, with abdominal discomfort and pain.[24] After discussions with the FDA, Incyte chose to supplement the phase 3 study primary endpoint on the reduction in spleen size with a newly-developed disease-specific patient-reported outcome (PRO) questionnaire. This led both to faster regulatory approval and better HTA and reimbursement outcome in countries such as Germany where patient experience is an important decision criterion.

2. **Optimal market access:** Companies successful in the rare disease space start planning for health technology assessment (HTA) early on. Crucially, do not look solely at clinical data but include patient centred endpoints, as noted above, and anticipate payer concerns. Prepare early in the development process (i.e. PIII or earlier) for RWE studies, which could include, pre-approval, studies on the epidemiology and natural history of the disease, unmet needs and current treatment pathways, and have them run alongside/as a part of development. This can create additional economic and patient data to support discussions during the HTA process. Investment in real world as well as clinical evidence builds connections to a broad range of stakeholders, critical to ensure the health system prepared to for optimal product uptake.

3. **Optimal product uptake of the approved market accessible population:** The concept of market access as health system readiness for the introduction of an agent in addition to market access as budget access is critical to rare disease Launch Excellence. This means a combination of an identified patient pool, worked out and established care pathways, pro-active and detailed assessment of and mitigation plans to address the burden to the healthcare system and company focus on patient support to address remaining bottlenecks (accessing reimbursement, time to approval and treatment).

In the following section, we delve into three critical dimensions instrumental to achieving Launch Excellence for rare diseases: Health system readiness, Stakeholder engagement and Value and evidence (Figure 9). The Three Pillars of Post-Pandemic Launch Excellence described in our Launch Excellence VIII study[25] reflect the new imperatives needed to thrive in the current environment. We further evolved and refined these to the rare disease area where the stakes are high and care pathways are even more complex and resource intensive. With health systems

Figure 9. Three pillars of rare disease launch excellence



Source: IQVIA EMEA Thought Leadership

under stress and enablers for orphan market access at risk, rare disease innovators must prepare early, effectively and with great attention to partnerships with stakeholders across all three pillars.

HEALTH SYSTEM READINESS

Many health systems are not ready — financially or operationally — to adopt innovation efficiently, particularly where the numbers of patients benefiting may be low. There is a growing 'innovation readiness gap' which disproportionally affects rare disease treatments as these are most likely to have the challenging combination of difficult-to-find patients, complex care pathway needs, and high per patient healthcare system costs. To address this, rare disease companies must diligently work towards understanding the patient journey in the context of each country's healthcare system. Many rare diseases affect young children and have genetic origins, so companies must aim to support early diagnosis, for example by advocating for genetic screening programs for newborns.[26] Patient support programs, telehealth or providing aid in patient transportation can help often fragile patients to manage their disease in stressed health systems. As a part of market building activites, new roles must be created dedicated to health system partnering/enablement. These are not part of common go-to-market capabilities.[27]

A highly successful U.S. rare disease launch by an EBP company, Horizon (subsequently acquired by Amgen) was Tepezza for thyroid eye disease. This 2020 launch coincided with the initial phase of the COVID-19 pandemic. Although Tepezza was a first-ever treatment for an unpleasant condition and the approval was highly anticipated, the treatment was delivered by infusion once every three weeks, posing a burden on both patients and healthcare systems. Horizon was unlucky to be launching Tepezza during the initial stages of the COVID-19 pandemic, when lockdowns challenged healthcare systems from diagnosis to delivery, with ophthalmology offices closing and healthcare systems in emergency mode. Horizon responded to this challenge with a combination of awareness raising and patient activation through early Direct-to-consumer (DTC) activities, which are allowed in the U.S., but unusual to be used this early in a launch, and digital engagement with healthcare professionals In addition, to address the environment of the immediate pandemic where hospitals were occupied with COVID patients, Horizon worked on strong real-world infrastructure in the form of a network of 1,000 infusion centres to deliver Tepezza to patients. This rapid pivot to virtual and direct to patient engagement resulted in a notably strong launch even in the difficult circumstances of the pandemic, and whilst some aspects (the very early DTC) were circumstance-specific, the combination of effective use of virtual engagement with delivery in a strong real-world network was a powerful driver of effective product adoption.

A recent gene therapy launch in the U.S. for the rare skin disease dystrophic epidermolysis bullosa, approved by the FDA in 2023, illustrates how convenience of treatment and reducing healthcare burden can be powerful to drive optimal product uptake. The product, Vyjuvek from the U.S. EBP company Krystal Biotech, was both the first treatment for the rare and debilitating skin condition, and therefore automatically addressing high unmet need, but it was also the first topical gene therapy ever approved, being a genetically modified herpes simplex type 1 virus which delivers copies of a missing gene when applied directly to the wounds which sufferers experience as a result of the fragile skin caused by their genetic defect. This highly novel approach to delivering gene therapy immediately removes the otherwise very high barriers to gene therapy use described earlier and places a significantly reduced burden on healthcare system capacity. However, Krystal Biotech is also pushing further, with an eye drop formulation for ocular complications of the condition planned. In addition, Krystal Biotech has sought to decrease time to treatment initiation for patients. Whilst it currently takes about 30 days for treatment to be started post reimbursement approval, Krystal plans to reduce this time by approximately half. The company's Krystal Connect support service includes, for the U.S., Patient Access Liaison teams to support patients in accessing coverage for the medicine. As at February 2024, Krystal Biotech reported that 35% of eligible dystrophic epidermolysis

bullosa patients, initiated start forms, and 19% had been granted reimbursement approval in the U.S. The launch, even in its early stages, is considered strong.

STAKEHOLDER ENGAGEMENT

Building great relationships, especially with patients, caregivers, patient organizations, and external experts, is of utmost importance from the earliest stages of development of a rare disease medicine. Small numbers of key opinion leaders and treatment centres can be very influential and hold rich real-world data. A factor which has proven, time and again, to be key to the successful development of orphan medicines has been early cooperation with Patient Advocacy Groups (PAGs) to work towards mutual goals. These can include the development of patient registries, data standards, trial design and endpoints, and healthcare system readiness for access and uptake post-approval. In one case, developed by IQVIA into a white paper with the support of the patient advocacy group, it was the patient advocacy group itself, the Alkaptonuria (AKU) Society, which was key to the creation of a consortium including key clinical experts and advocates, specialist hospitals, and the pharmaceutical company who was the original owner of the pharmacotherapeutic that successfully developed and brought Orfadin (nitisinone) to approval and use for Alkaptonuria.[28]

Cross stakeholder cooperation is also critical to develop rare disease registries which are valuable for multiple clinical trials and multiple aspects of clinical development for orphan medicines. In the U.S., the Cystic Fibrosis Foundation built, over multiple decades, a patient registry of the vast majority CF patients in the U.S., which has been used for clinical trial design and recruitment, post market surveillance and other real world data development.[29]

Medical Affairs (MA) has a deep understanding of the health system and its stakeholder environment. In rare diseases, MA and its highly valued scientific communication is even more critical and must be considered pre-launch. Thus, enabling medical-led engagement early in an asset's life to explain a novel mode of action and in return, also generates valuable insights into HCP viewpoints and future educational needs. Pre-launch activities moreover will also include supporting discussions with PAGs, external experts, payers, HTA bodies or policy makers. Post-launch, medical engagement is perceived as more valuable by HCPs and must be integrated in cross-functional teams to deliver an education journey centred around compelling evidence.[30]

VALUE AND EVIDENCE

An integrated evidence strategy, that is, the strategically planned combination of clinical and real-world evidence (RWE) from pre-launch and across the launch and lifecycle of a product, is mission-critical in the field of rare diseases. Rare disease innovators must understand and evidence disease epidemiology, starting with accurate incidence and prevalence figures. Understanding true prevalence and incidence figures can be vital in making the case for health system priorities, as orphan medicines are generally perceived as high cost, to the point where treating 50 vs. 100 makes a major difference.

Accurate patient numbers reassure payers and allow budget planning for swifter access. RWE generation helps insight on complex disease biology and the natural history of the disease and can lay the basis for better patient finding. A particular challenge arises for therapies with curative potential, as many gene therapies for rare disease promise to be. The first challenge is addressing the question of whether a therapy is truly curative, with lasting impact the whole life of the patient. As gene therapies are most often administered to very young children, there is no gene therapy that has in practice demonstrated whole life curative impact, and of course it would be impracticable to wait until a gene therapy had done so before granting approval and budget access if the initial outcomes are positive. However, Health Technology Assessors have the challenge of valuing a treatment which may not be whole life curative, and value to patients for whom, if a gene therapy's effects wears off after a number of years, alternative non gene therapy will then be required. In some instances, notably haemophilia, whilst a gene therapy is available, uptake has not been as strong as anticipated, with potentially eligible patients opting for existing, non-curative chronic treatment instead (it is worth noting that haemophilia is a condition which can be managed and lived with lifelong, unlike rare genetic conditions which are gene therapy candidates which cause early progressive deterioration and death). This can be because of a combination of convenience, but also reluctance to use gene therapies perceived as not fully proven and with the possibility that earlier iterations of gene therapy may not be as good as later developments. The evidence strategies for curative therapies for rare disease patients are, therefore, exceptionally complex and an ongoing challenge. Any company with a curative treatment for rare disease must be on top of the latest developments in curative therapies across all rare disease areas as well as having depth insight into decision-making by patients and payers within their own disease areas in response to course of disease and treatment options and windows of opportunity.

Orphan medicines can be approved on immature data from single-arm trials without a control group, thus making RWE collection a requirement post-approval by HTA bodies to support early access. Assessing the most appropriate source for collecting RWE is important and could include e.g., patient and product registries, electronic health records, claims and pharmacy data and importantly, patient-generated data, e.g., on quality of life and functional improvements. Collectively, leveraging RWE can help support throughout a product's lifecycle by providing relevant, evidence-based content to educate systems, doctors, payers, and health technology assessment bodies.

Structure for success

EBPs are responsible for the majority of the rare disease pipeline, and commercialisation of orphan medicines by EBPs is increasingly common — over the last decade, the share of orphan medicines launched in the U.S. that were commercialised by EBPs has risen from 26% in 2014 to 55% in 2023 (Figure 4). Mid-sized and large pharmaceutical companies have also been increasingly active in the rare disease space over the past decade. This poses a strategic question: how to run a successful rare disease business in the context of a much larger, multi-portfolio company, and how to build a successful multi-product portfolio as an EBP?

EBP companies launching rare disease products often are doing so for the first time, and must build the plane while flying it. Often, tight funding necessitates focus on the essentials, which means expensive clinical development, at the expense of what can be perceived as optional, for example, real world studies, early pre-launch investment in Medical Affairs. However, orphan medicine launch success stories show that pre-launch investment in market preparation, via stakeholder engagement using Medical Affairs, or investment in Real World Evidence, for example, is a critical factor for earlier and better launch success. Typically, IQVIA has found that EBPs tend to be a year behind their large pharmaceutical company peers on non-clinical pre-launch investment. A critical skill for EBPs is to identify what non-clinical pre-launch investment is essential and secure funding for it. Read more about IQVIA's Launch Excellence Framework in our case study below:

Case study

Situation

Launch Excellence can be achieved by an emerging biopharma (EBP) company in rare diseases, but EBP companies start launch preparation with fewer resources and often later (typically by a year) than large pharma companies. In this case study of an EBP company preparing their launch in a rare disease, the main challenges in launch planning and readiness were related to:

- A lack of definition of roles and responsibilities
- Limited visibility across teams (i.e., global, regional, local, and functional teams)
- A launch plan and tools that didn't enable an integrated and cross-team/functional tracking
- A lack of well-defined processes to effectively mitigate risks and issues

Solution

IQVIA worked with the EBP company to develop a detailed launch plan by leveraging the IQVIA launch excellence framework. Because EBP companies lack the resources of large pharma for pre-launch preparation they typically start later on launch preparation and require a tailored and pragmatic prioritisation. Therefore, a matrix was built to prioritise launch activities/milestones based on the impact on the launch performance and timeline criticality. The result was a slimmed down, simplified framework, focused on the essentials for an effective launch preparation.

From a change management and communication perspective, the first focus was on people alignment to roles and responsibilities. A change management and communication plan were developed to support with the deployment and adoption of launch operational changes.

Impact

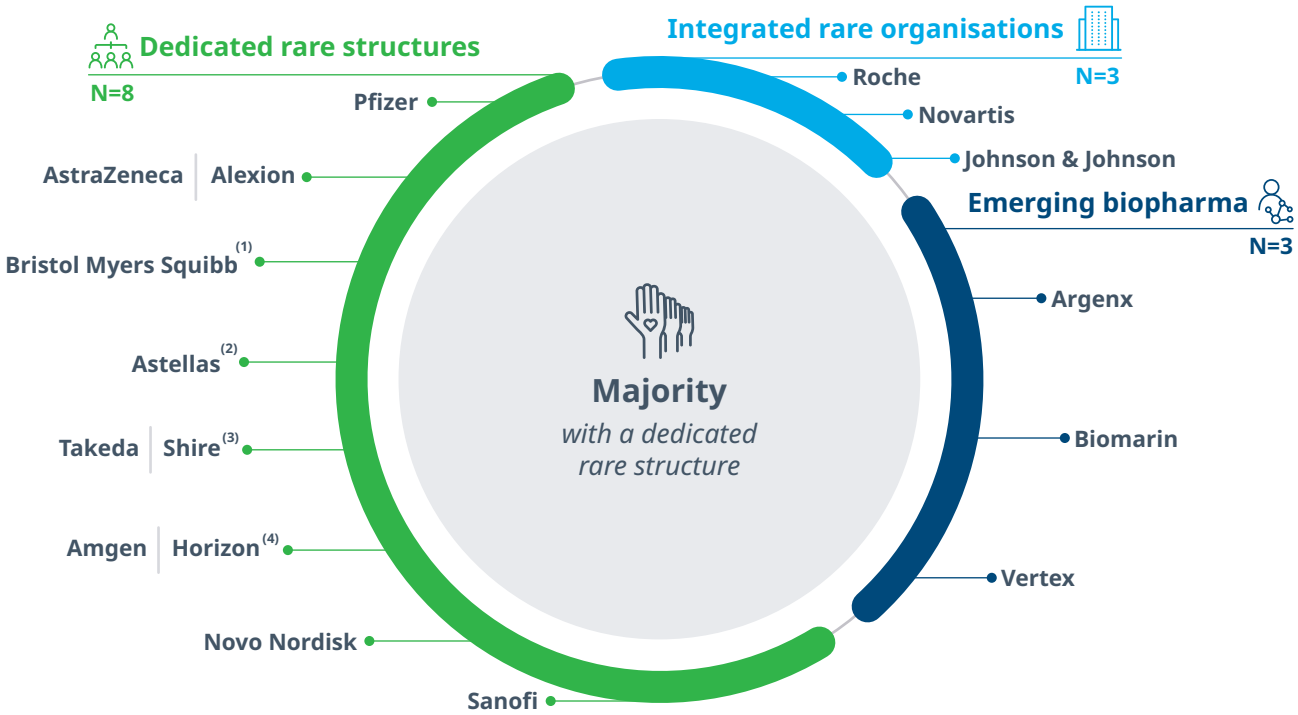
A Launch Excellence toolkit including a detailed launch plan, with cross-functional launch activities and key resources and interdependencies, was deployed to the launch team. This was accompanied by a change management roadmap to address people and organisational challenges that are intrinsic to the DNA of EBP companies, necessary to support the execution of a successful launch.

A common situation is the U.S. based EBP, which launches its rare disease product itself in the U.S. and then addresses the European market as the second region to launch, but must face the challenge of a multi-country region with very different dynamics to the U.S. Despite the challenges of market access and multiple countries, the barriers to European entry are lower and more readily surmountable than many companies perceive, and IQVIA addresses this in the white paper Realising the Commercial Promise of Europe for Emerging Biopharma,[31] outlining the decisions companies have made on European structure and investment for success.

Whilst EBP players often benefit from focus and specialisation, large pharma, whilst possessing advantages of scale and deep pockets, risk losing focus and depth expertise in addressing the unique needs of rare diseases. More large and mid-sized pharmas have addressed this challenge through the creation of dedicated rare disease structures (which in some cases came from the transformation of rare disease acquisitions) than have created integrated rare organisations, although these exist for companies that have been highly successful in the rare disease space. Successful commercial EBP players in rare are most often rare disease specialists, with a portfolio in rare, sometimes, as in the case of Vertex in cystic fibrosis, in the same condition over multiple products (Figure 10).

There's no single solution to company structure as history, company culture and other factors will also play a part, but behind the different organisational approaches, it's clear that the important underlying principles for rare disease success are focus and depth expertise, combined with long term commitment and dedicated resources.

Figure 10. Selection of rare disease company structures



1. Legacy Celgene (haematology franchise) is a separate TA business unit reporting into the CCO
2. Astellas Gene Therapies acts as its own entity
3. Restructuring as current model of treating rare as other TAs is not working
4. Acquired by Amgen; no official status from on structure

Source: IQVIA EMEA Thought Leadership

Conclusion

The U.S. Orphan Drug Act, designed to encourage the development and launch of treatments for rare, neglected diseases, was first enacted in 1983, over 40 years ago. The EU Orphan Regulation was initiated in 2000. As these critical kickstarters for today's modern rare diseases market approach their half century and quarter century respectively there are more launches into rare diseases than ever before, and the current pipeline productivity is highly likely to continue. Rare disease launches were amongst the most resilient in the immediate pandemic and post-pandemic launch environment, but the environment is changing; payers are decreasingly likely to automatically treat rare disease launches as special cases in terms of market access, health technology assessors are increasingly sophisticated and discriminating in their assessment of orphan medicines, and policymakers see orphan medicines as an integral element of their reforms of medicine policies on access and affordability.

Despite the successes bringing orphan medicines to market of the past decades, as noted in the introduction, it was recently estimated that of the 7,000-10,000 rare diseases that have currently been described, only 5% have an FDA-approved pharmacotherapy.[32] The development and introduction of orphan medicines remains therefore a key unmet need of global healthcare provision. The research and development pipeline for rare diseases remains robust, driven by the heterogeneity of the rare diseases themselves, technology platforms and the companies (both EBP, mid and large pharma) that are actively engaged in the rare disease space. Exciting developments in underlying technologies arise — for example CRISPR-based editing of cells, as in Casgevy (exagamglogene autotemcel), designated an orphan medicine in the EU for beta thalassemia and sickle cell disease. These in turn raise challenging health equity questions, as in sickle cell disease, where the majority of patients live in countries which will not have access to the funding or facilities to use these leading-edge therapies in the foreseeable future. Rare cancers and genetically driven conditions will continue to be important elements of the rare disease pipeline, but in the future, rare conditions in cardiovascular, neurology and immunology (which may also have genetic origins) will also see launch numbers grow.

Rare disease launches are an environment in which conventional wisdom on drug development and launch has repeatedly been challenged, successfully. The work of the AKU Society to drive the development of the first pharmacotherapy for alkaptonuria created a new paradigm for partnership in developing treatments, one where the Patient Organisation was the driver, not the pharmaceutical company. This was and will remain a highly unusual approach to the development of an orphan medicine, but the story of the challenges that we addressed to successfully bring this product to market hold lessons for other, commercially driven rare disease launches. The actions of Horizon when launching Tepezza, albeit in the unusual circumstances of the pandemic, demonstrated that mass direct-to-patient engagement and creating infrastructure outside the established health system can power exceptionally rapid patient uptake.

The future launch environment for rare disease launch will undoubtedly be more challenging, but the fundamentals in terms of underlying need and promising technologies is strong. Companies planning their rare disease launch should follow these golden rules (Figure 11):

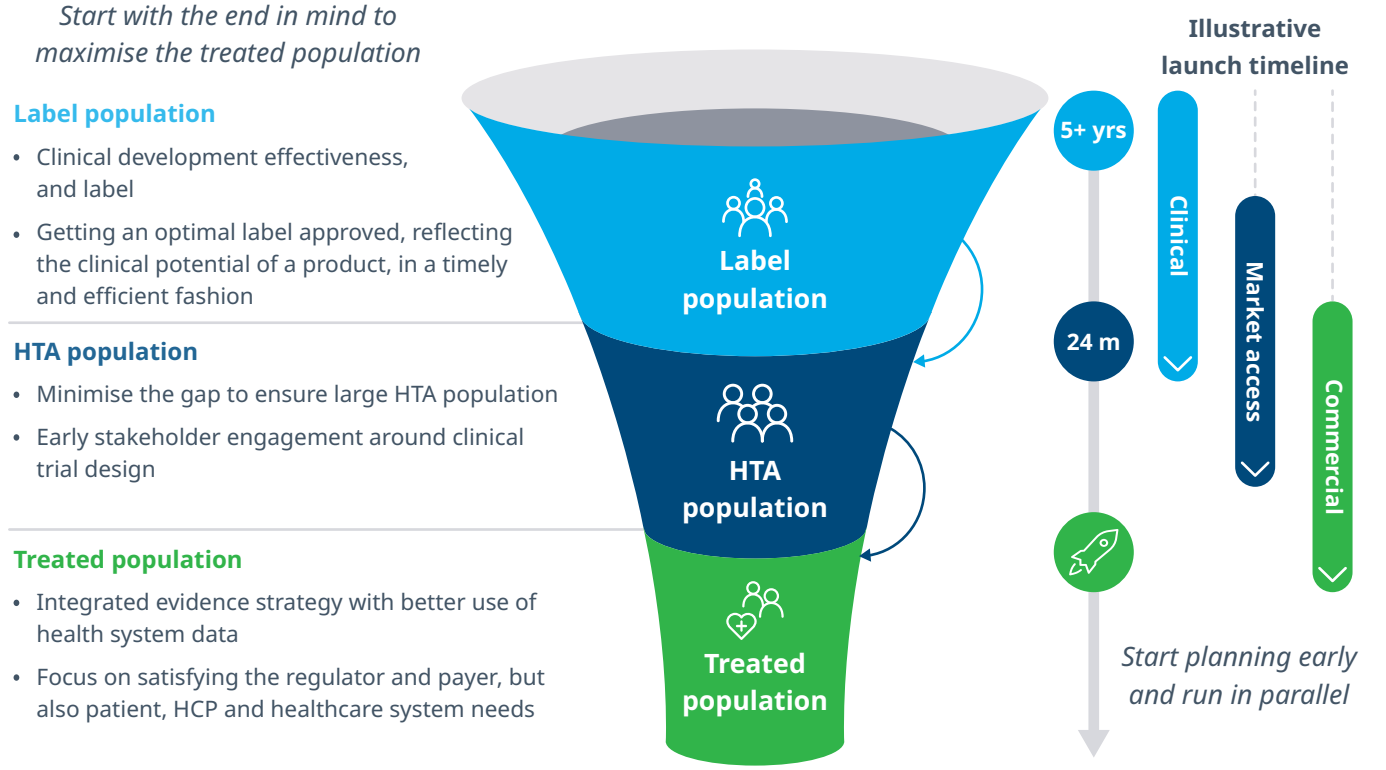
1. Start early and with the end in mind, as soon as the potential label on approval becomes apparent. This may be when an asset has entered Phase II trials and looks likely to enter Phase III, or when breakthrough designation is granted. Plans to maximise on the three levels of rare disease population: the label population, the market access (funded) population, and the treated population should run in parallel not sequentially, because preparing the health system to be ready to bring your orphan medicine to the treatable population may take years working with healthcare system stakeholders. Early investment in Medical Affairs, in planning Real World studies to run alongside clinical studies, and to engage across the healthcare system stakeholders as early as possible is critical.

2. Throughout development, launch preparation and launch, to address these populations, focus on the three pillars of rare Launch Excellence, that is, early and effective Stakeholder Engagement, Healthcare system preparation for launch readiness, and building the Evidence for Value story. While common to non-rare launches in the challenging post-pandemic launch environment, these three pillars require particular focus and interpretation for rare diseases.

3. Lastly, do not be afraid to break with convention. Rare diseases, and the development of the orphan medicines to treat them, break paradigms because they create unusual and challenging situations. Successful companies therefore must be flexible, agile, and unafraid to think outside the box to achieve the ultimate goal of bringing orphan medicines to market.

Successful rare disease launches are never only a simple consequence of a pharmacotherapeutic breakthrough meeting a significant unmet need. Companies behind successful rare disease launches have consistently demonstrated meticulous, early focus on understanding the condition their product targets in exhaustive detail, engaging early with patients, their carers and patient advocacy groups, clinical experts and stakeholders, healthcare systems and payers.

Figure 11. Addressing the three populations of rare disease opportunity



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