PHARMA BOARDROOM

InFocus
Rare Diseases

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2019

In collaboration with: sobi rare strength

Sobi is an international rare disease company dedicated to providing access to innovative treatments that make a significant difference for people with rare diseases. We have two business areas: Haemophilia and Specialty Care. Our research and product portfolio is primarily focused on haemophilia, inflammation, and genetic and metabolic diseases.
The United Kingdom and Republic of Ireland team is based in Cambridge and have been rated as one of the UK's great places to work in 2017, 2018 and 2019.

At Sobi, we refuse to accept the status quo. This is because we have witnessed first-hand the challenges facing those affected by rare diseases, and have used this knowledge to shape our business to find new ways of helping them. As a specialised biopharmaceutical company, we are dedicated to rare diseases. And we see this focus as a strength. By effectively turning our clinical research into ground-breaking treatments, we help make medicine more accessible and open up more possibilities for patients and more opportunities for those caring for them.

This has been our approach since day one, but we know we can't change the world of rare diseases on our own. Accomplishing this requires strong partnerships with patients, partners and stakeholders across the entire value chain. Together, we define how our business can create solutions that serve the needs of those affected by rare diseases while facilitating sustainable growth.
We bring something rare to rare diseases – a belief in the strength of focus, the power of agility and the potential of the people we are dedicated to serving.

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rare **strength**

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For exclusive interviews and more info, please log onto www.pharmaboardroom.com or write to contact@focusreports.net.

Long regarded as a neglected backwater within the drug discovery landscape and the preserve of only a handful of niche players, the rare disease space has been undergoing an extraordinary turnaround in fortunes of late.

Going Mainstream

Orphan drug sales are set to grow 11 percent annually to 2024, significantly outpacing the overall pharma market, which is set to expand a mere 6.4 percent over the same period. Moreover, by 2024, orphan drugs are predicted to constitute a fifth of all prescription sales, generating some USD 262 billion worth of revenues worldwide, making rare disease therapies some of the hottest property within the entire industry. Currently, only five percent of rare diseases have treatments, representing an enormous opportunity to meet unmet medical need.

Little wonder, therefore, that the segment has gone mainstream and is now dominated by the same big pharma brands that once eschewed it. "Developing drugs for rare diseases, once considered a rare phenomenon itself, has fast become an orthodox strategy for many companies' drug development pipelines," says Gayatri Rao, director of the US FDA's Office of Orphan Product Development. What could have triggered such a dramatic change?

RARE DISEASES BY THE NUMBERS

50%

OF THE PEOPLE AFFECTED BY RARE DISEASES ARE CHILDREN

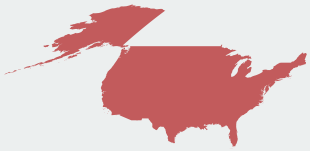
APPROXIMATELY 7,000

RARE DISEASES & DISORDERS HAVE BEEN IDENTIFIED

IF ALL OF THE PEOPLE WITH RARE DISEASES LIVED IN ONE COUNTRY, IT WOULD BE THE

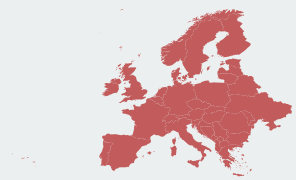
WORLD'S 3RD MOST POPULOUS

COUNTRY



30 MILLION

PEOPLE IN THE US ARE LIVING WITH RARE DISEASES



30 MILLION

IN EUROPE ARE LIVING WITH RARE DISEASES

Regulatory Game-Changers

The 1983 Orphan Drug Act (ODA) in the USA has often been pinpointed as the game-changing moment when rare disease drug development suddenly became lucrative. In a bid to alleviate market failure, the legislation awarded incentives for pharmaceutical companies ordinarily reticent to invest in drugs which only served tiny patient populations. These included tax credits to defray the costs of R&D, privileged approval times, seven years of market exclusivity, clinical trials subsidies and reduced regulatory fees. Other regulatory agencies ultimately followed suit with the EU passing an equivalent bill in 2000.

Meanwhile, a proliferation of the deployment of auxiliary or surrogate endpoints within clinical trials for orphan drugs has significantly alleviated the time and expense required for conducting R&D, because they apply substantially lower thresholds for indicating treatment success.

"The way to make big bucks from medicines conventionally used to be to develop a blockbuster commodity drug, such as a remedy for high blood pressure or elevated cholesterol. Used every day by millions, it was a sure route to profits. Now, increasingly the way to be sure of generating a strong return on investment is to conceive a treatment for one of the hundreds of rare diseases for which there is no cure. The actual pool of patients who can benefit may be tiny, but for that group, it will be life-changing or life-saving," explains Sarah Neville of the Financial Times.

> "THE ACTUAL POOL OF PATIENTS WHO CAN BENEFIT MAY BE TINY, BUT FOR THAT GROUP, IT WILL BE LIFE-CHANGING OR LIFE-SAVING"

Gaming the system

Many drug developers have become adept at manipulating the rules of the game to acquire orphan status for therapies with more widespread potential usage. Under FDA terminology, there are approximately 6,800 rare diseases in the world and, to be considered a rare disease, a condition must affect fewer than 200,000 Americans.

Many drugmakers, however, have been accused of "salami-slicing" – applying for multiple orphan drug approvals for a single drug by splitting a prevalent disease into smaller subcategories, often characterized by genomic biomarkers. "Some of the world's bestselling drugs notched initial approvals for diseases with broad patient populations and then, when the drug developers applied for approval in rare diseases, brought in benefits such as tax breaks and monopoly pricing power," reflects FiercePharma's Eric Sagonowsky, highlighting AbbVie's Humira, and Roche's Herceptin.

Time to Break the Rules?

In view of these loopholes, there is increasing suspicion that orphan drug status may no longer be fit for purpose. Nicholas Bagley of the Institute for Healthcare Policy and Innovation points out that "the incentive structure is an especially poor fit for orphan drugs that target such rare conditions, or are so challenging to manufacture, that the market will not support similar products from multiple firms because these natural monopoly drugs will never face meaningful competition and so would likely prove highly lucrative even without the ODA benefits."

Payers doubtless agree that the moment is ripe to review the system, especially given the high price tags of some orphan drugs. Spark Therapeutics' Luxturna, a gene therapy approved by the FDA in 2018 designed to treat patients with a rare form of inherited blindness, for example, comes in at USD 425,000 per eye (so USD 850,000 per patient), making it the most expensive pharmaceutical in the USA.

Already regulators are making preliminary moves to introduce greater fairness into the process. "The once protected island orphan drugs represented for drugmakers may well suffer some erosion as payers become emboldened to take on pricing in areas that were once too small to risk the public relations damage of doing so," warns Daniel Levine of Global Genes.

> "THE FOCAL POINT OF BIG PHARMACEUTICAL PLAYERS' EFFORTS IS GRADUALLY DRIFTING FROM BLOCKBUSTER TO NICHE-BUSTER."

Aligned with Science

The rare disease space does not, however, stand to lose its lustre any time soon. All the signs point to it being highly aligned to the new world of medical science. The maturation of personalized precision medicine, big data and genomics is allowing for more effective targeting of difficult to diagnose and treat disease forms, while an improved understanding of the genetic basis of pathologies is unlocking the ability to define and target rare disorders.

Moreover, the underlying rationale of striving for orphan status in an era of austerity and ever-greater belt-tightening should not be underestimated. "Focusing energies on rare diseases affords drug makers an unparalleled opportunity to generate convincing clinical safety and efficacy data with very limited patient populations, which can translate to a quick path to regulatory approval, which in turn means the cost of development will be a fraction of what it could be for more common diseases," reasons James Wilson of the Orphan Disease Center at the University of Pennsylvania. "The focal point of big pharmaceutical players' efforts is gradually drifting from blockbuster to niche-buster."

TOP 10 ORPHAN DRUG COMPANIES RANKING

Ranked by global orphan drug sales (USD billion) and market share in 2017

Rank	Companies	Sales (USD millions)	Market share (%)
1	NOVARTIS	12.4	9.9%
2	ROCHE	10.3	8.2%
3	CELGENE	10.0	8.0%
4	SHIRE	7.8	6.2%
5	BRISTOL-MYERS SQUIBB	7.3	5.8%
6	MERCK & CO.	5.3	4.2%
7	JOHNSON & JOHNSON	5.0	4.0%
8	PFIZER	4.9	3.9%
9	SANOFI	3.9	3.1%
10	ALEXION PHARMACEUTICAS	3.5	2.8%

Source: Evaluate Pharma May 2018

RARE DISEASE DEFINITION BY REGION

Source: EvaluatePharma May 2018

Rare Disease Patient Populations are Defined in Law as:

USA

<200,000 PATIENTS

(<6.37 IN 10,000, BASED ON US POPULATION OF 314M)

EU

<5 IN 10,000

(<250,000 PATIENTS, BASED ON EU POPULATION OF 514M)

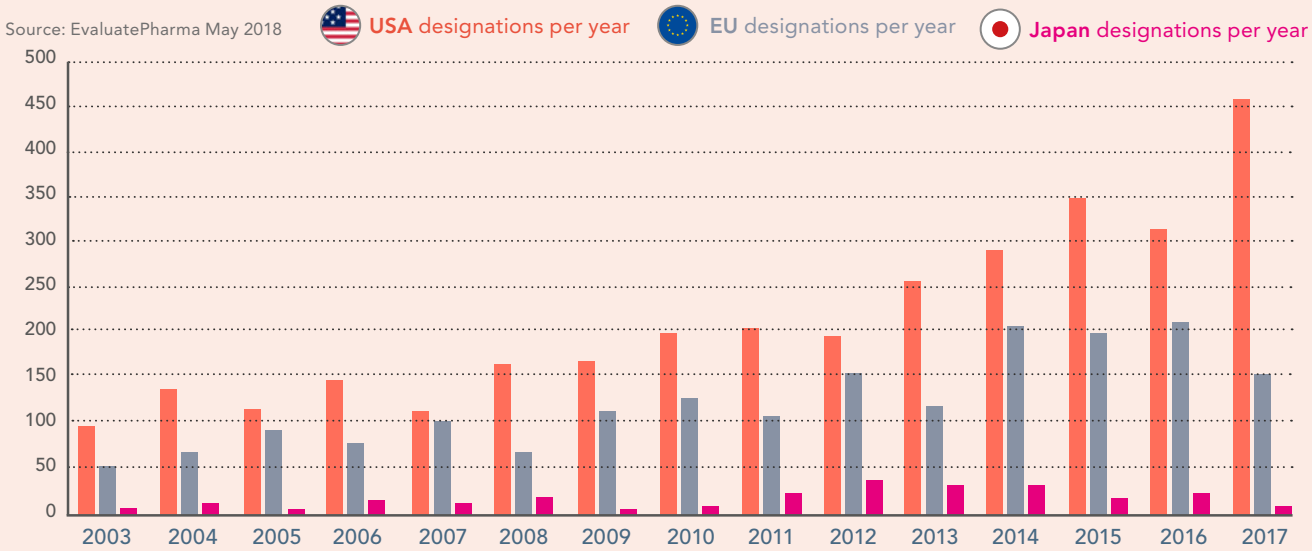
JAPAN

<50,000 PATIENTS

(<4 IN 10,000 BASED ON JAPAN POPULATION OF 128M)

USA, EU & JAPAN ORPHAN DESIGNATIONS PER YEAR (2003-2017)

Source: EvaluatePharma May 2018



TOP 10 ORPHAN DRUGS IN THE USA

	Drug	Drug Manufacturer	USA Sales (USD mn, 2017)	Revenues per patient* 2017	No. of patients
1	Revlimid	Celgene	5,426	184,011	29,847
2	Rituxan	Roche	4,199	65,009	64,594
3	Copaxone	TEVA	3,116	60,906	50,061
4	Opdivo	BMS	3,102	43,847	70,746
5	Keytruda	Merck (MSD)	2,309	56,910	40,573
6	Imbruvica	AbbVie	2,144	126,820	16,906
7	Avonex	Biogen	1,594	78,262	20,367
8	Sensipar	Amgen	1,374	6,287	218,559
9	Soliris	Alexion	1,235	501,719	2,462
10	Xyrem	Jazz Pharmaceuticals	1,187	81,624	14,539

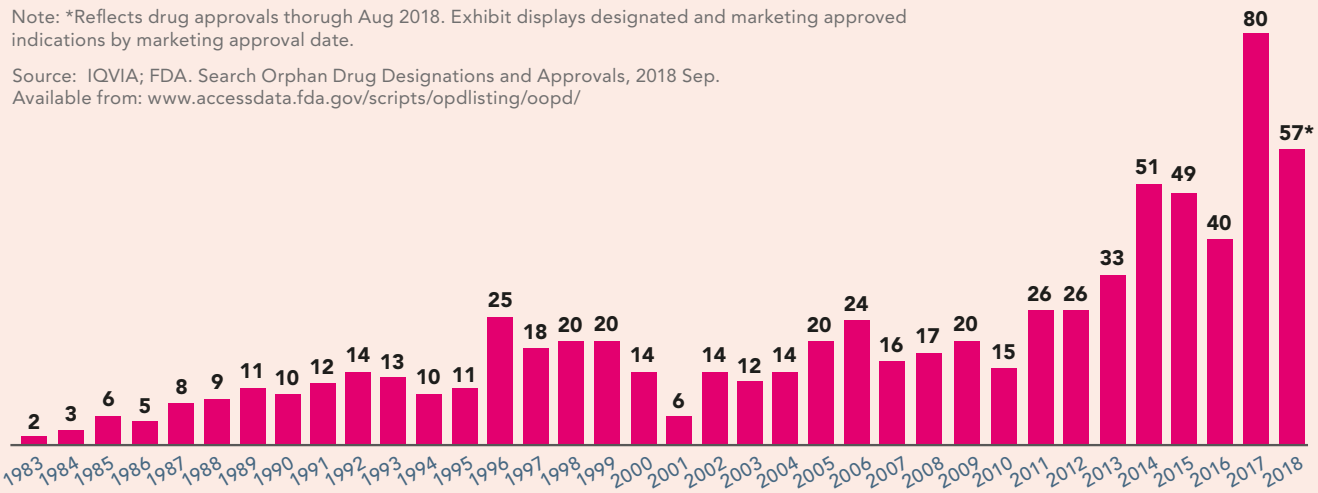
*Revenues per patient: An estimate of the dollar ($) revenues per year received, by a company, per patient for drug in the USA market. This takes into account the cost per patient (average mg per year multiplied by the cost per mg), off-invoice discount and patient compliance.

Source: EvaluatePharma May 2018

NUMBER OF ORPHAN INDICATIONS APPROVED IN THE UNITED STATES (1983-2018)

Note: *Reflects drug approvals thorugh Aug 2018. Exhibit displays designated and marketing approved indications by marketing approval date.

Source: IQVIA; FDA. Search Orphan Drug Designations and Approvals, 2018 Sep. Available from: www.accessdata.fda.gov/scripts/opdlisting/oopd/



ORPHAN DRUGS IN CONTEXT

- Only **9.6%** of all drug spending in the United States is attributed to orphan indications.
- Of the **$99.5 billion** increase in specialty spending over the last five years, specialty orphan drugs contributed about **$17.5 billion** of growth and non-orphan specialty drugs contributed the remaining **$82.1 billion.**
- Specialty orphan drugs contributed less than **18%** of growth from 2012–2017 with the bulk of growth deriving from medicines with annual costs in excess of **$6,000.**

Source: IQVIA

- In 2017, less than **1%** of total volume of drugs was the result of orphan therapies being used according to their orphan indications.
- Since 1983, **78%** of orphan drug approvals have included orphan-only indications, and the remaining **22%** have approvals for both orphan and non-orphan indications.
- Despite an increase in the number of orphan drugs available on the market, the total volume of orphan drugs has declined over the last ten years, though the last three years have shown growth.

A NEW APPROACH TO CLINICAL TRIALS

Drug development in rare diseases is currently in a very exciting time. While much of the focus is on the scientific advances, access to rare disease patients and well-designed clinical trials are also essential to evaluating new therapeutics.

PJ Brooks, program director at the Office of Rare Diseases Research of the National Institute of Health (NIH) in the US and his two colleagues — Tiina Urv and Anne Pariser — highlight the Rare Diseases Clinical Research Network (RDCRN) as a platform for carrying out clinical trials in multiple rare diseases concurrently, rather than the traditional one-disease-at-a-time model.

The impetus of the RDCRN was the Rare Diseases Act of 2002 (Public Law 107-280) which included language specifically directing the NIH to establish centres of excellence for the study of rare diseases. The first iteration of the RDCRN was initiated in 2003. The program is supported through partnerships with multiple NIH Institutes and Centers and is coordinated through the Office of Rare Diseases Research at NCATS.

The RDCRN consists of individual consortia that study at least three different rare diseases. Each consortium consists of researchers, clinicians, patient advocacy groups (PAGs), patient representatives, and NIH scientists working as partners. The broad focus of the Network is to advance the diagnosis, management, and treatment of rare diseases through highly collaborative, multi-site, patient-centric, translational and clinical research with a narrower focus on addressing unmet clinical trial readiness needs. The consortia are also connected through a common Data Management and Coordination Center, tasked with data collections, data standards, and other support such as protocol assistance and oversight.

The current cohort is currently completing its third funding cycle. As of Sept 2018, the RDCRN consists of 21 research consortia, studying approximately 200 rare diseases. The consortia are diverse and include those centred around a particular organ, an organelle (e.g., mitochondria, lysosomes), phenotypes, and other unifying concepts. Collectively, there are 128 accruing NIH-approved protocols in 278 Institutions throughout the world. For some rare diseases, this international coverage is crucial to access sufficient numbers of patients for clinical studies.

Through the structure provided through the RDCRN uniform data, collection protocols have been made possible and the RDCRN has been able to establish meaningful,

PJ Brooks
program director, Office of Rare Diseases Research, National Institute of Health, USA

large-scale clinical studies in rare diseases. In addition, the RDCRN trains new investigators in clinical rare disease research, which is quite different than working in more common diseases. For example, training in innovative study designs and the de novo development of clinical trial elements, such as outcome measures, are usually needed for rare disease research.

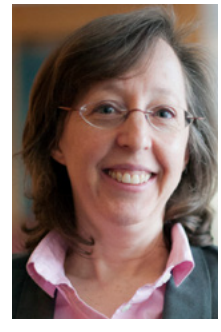
Throughout its existence, two key features of the RDCRN have been the engagement with PAGs and requirement for longitudinal natural history studies in rare diseases. The requirement for participation of PAGs reflects the reality that for rare diseases, strong working relationships with PAGs are essential for initiating and carrying out and completing effective clinical trials.

The second key feature of the RDCRN is the requirement for longitudinal natural history studies in rare diseases. For an adequate and well-controlled clinical trial, valid clinical outcomes measures are essential, and the best outcomes measures are those derived from careful evaluation and understanding of disease natural history obtained through good quality natural history studies. Despite this, there are real challenges in funding natural history studies in rare diseases, due in part to the fact that proposals are open-ended, typically require long-term funding, and often evolve over the time-period of their conduct (such as design changes). These studies often do not do well in standard NIH review panels, in part due to the uncertainty in outcomes, and are often not viewed as innovative. To address these challenges, the requirement for at least one longitudinal natural history study in every Award has been a requirement since the inception of the RDCRN.

The value of natural history studies supported by the RDCRN can be seen in recent clinical trials of genome editing in Hunter syndrome and Hurler syndrome. Both syndromes are rare lysosomal storage diseases that have been under study by the Lysosomal Diseases Network (LDN). Clinical investigators from the LDN researchers worked with the company to develop the current clinical trial and recruit participants, and some of the centers involved in the trial are part of the LDN. As part of these trials, investigators will be able to assess the safety of the gene editing technique in patients and will evaluate effectiveness by using LDN-developed clinical tools, including brain imaging.

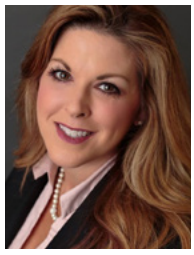
In summary, for the reasons highlighted above, we envision the RDCRN as a unique rare disease clinical trials platform. As we look forward to starting the next round of the RDCRN, we encourage those looking to evaluate novel therapeutics for the rare diseases we have under study to contact Dr Tiina Urv (urvtiin@mail.nih.gov) or one of the RDCRN principal investigators about the potential for collaborative efforts.

Tiina Urv
program director, Office of Rare Diseases Research, National Center for Advancing Translational Sciences, National Institute of Health, USA



Anne Pariser
director, Office of Rare Diseases Research, National Center for Advancing Translational Sciences, National Institute of Health, USA

> “WE ENVISION THE RDCRN AS A UNIQUE RARE DISEASE CLINICAL TRIALS PLATFORM”
>
> — **PJ Brooks** RDCRN



Monica Weldon
founder,
Bridge the Gap

MYTHBUSTING: PATIENT ACCESS

After her son was diagnosed with SYNGAP1 – an extremely rare gene mutation – Monica Weldon founded Bridge the Gap – SYNGAP Education and Research Foundation to support families of those suffering from the illness and to accelerate the path to better therapies. Here she busts several myths about getting to rare disease treatments.

MYTH #1: THROWING MONEY AT RESEARCH WILL GET US TO TREATMENTS FASTER

Some advocacy organizations do not understand the landscape of rare disease in general. This is to be expected if you or a loved one has just been thrown into the world of rare diseases. The lack of the basic understanding of how rare disease research and drug development work can be a huge factor in why progress is hindered. This lack of knowledge causes a severe deficiency in strategic planning.

Many organizations begin with the intent they will merely go out, apply for nonprofit status and fundraise to throw money at research, thinking that this will speed up the process of getting to treatments. Not so! Fundraising is only a small portion of getting to treatments. Yes, money helps, yet spending money strategically will benefit eliminating the challenges ahead. When you have uneducated people who do not understand the landscape, the chances of failing are high and can cost you YEARS in progress! There is a right way, and there is a WRONG way to approach getting to treatments. Understanding the nature of the disease and research is the first step.

MYTH #2: WE HAVE MODERN MEDICINE AND TECHNOLOGY

There is no doubt that modern medicine has improved the quality of life and extended life for many, but we still have a long way to go.

In rare disease, there are those unique challenges that we still have to overcome. When asking a group of rare disease leaders their opinions on why the needle hasn't moved their views were not off target. Many reported that regardless of the time they live, we still lack the necessary resources to speed up the process. There is a need for researchers in relatively new medical fields that focus on rare disease. Right now there are just not enough.

Another noted fact is due to a lack of diagnosis rates, which result in low numbers and scattered patient populations. Money raised by nonprofit organizations, in reality, is a drop in the ocean for being able to drive the research needed to get to treatments. The lack of funding for basic science research to understand the mechanisms of how disease even works is still required.

MYTH #3: OUR ORGANIZATION CAN'T ADVOCATE FOR POLICY CHANGES

False!

In 2016 npEngage reported that "only when lobbying activities become "substantial" does a possibility arise where your nonprofit status can be revoked. This means that nonprofits are permitted to lobby on a "limited basis," which equates to "20 percent of the first $500,000 of exempt purpose expenditures up to a cap of $1 million on total lobbying expenditures. Where this "fine line" is drawn often depends on the "federal administration in office". Essentially, this means that as long as you are not exceeding that 20 percent up to $1 million, it is fair game to engage in advocacy as a nonprofit organization." Under nonprofit advocacy/lobby rules, organizations can participate in certain activities that can provide the needed push to change policy.

Advocacy is critical to getting to treatments. There are so many diseases and not enough people and companies willing to invest resources. We have heard things like "it's not a serious illness," or "there's no money to be made in developing a treatment" – a common sentiment expressed in the rare community. However, it is one that can be overcome by the simple measures of understanding how policy affects drug development. No one will argue that in every circle of every business there is corporate greed. Policy changes can incorporate oversight and accountability to eliminate some of the "fleecing" of drugs overall.

Understanding the system is a complicated process, but not impossible. The US insurance and payer model discourages innovation and therapies affecting small disease populations. Pricing of drugs is not the sole issue. While 95% of all rare disease lack treatments, it is still critical for organizations to involve themselves in the policy process change. The reason is simple. Eventually, your hard work may pay off, and your disease will get to treatment. Making the drug you are after is only half the battle and gaining access to it is another.

Access defines how quickly a member/patient can get a drug. The majority of drug prices are set for more common diseases, like Augmentin for strep throat. It is based on supply and demand. The higher the demand, the higher the price. Low patient numbers create an issue with the current "formula" on how drugs are figured for reimbursement. Pricing formulas determine how much each entity handling the drug will get paid, for example, the hospital who houses it, your co-pay cost and what your insurance company will receive. Changes in recommended executive policies also is an area that needs addressing.

The issue remains that due to the lack of patient numbers it is difficult to get drug companies to invest in creating drugs for rare diseases. It's a huge gamble for them. All rare disease organizations in the United States should see it as a priority to help facilitate this change at the federal level. A more basic principle as to why is that in theory we are all connected in some form or fashion at the genetic or molecular level when it comes to disease. No genes act alone, therefore if one drug could help one disease then why not use that same drug for another indication?

WHY INVEST IN AND PURSUE ORPHAN DRUG OPPORTUNITIES?

David H. Crean of Objective Capital Partners outlines the benefits of investing in orphan drugs.

Hundreds of new rare-disease treatments have entered the market over the past few decades, and orphan drug development has become a highly profitable industry. Historically, these treatments have been a tough sell due to the small markets associated with them but vigorous patient advocacy, venture capital investment, industry collaboration, medical breakthroughs, and legislative incentives are dramatically changing the landscape of rare disease research.

The advantages of investing in orphan drugs are several-fold. There is a lack of competitors or strong competitive headwinds in the space. The main reason to develop an orphan is that most large pharmaceutical companies are discouraged from spending huge amounts of resources on what they consider a small group of patients, a minimum market.

Another benefit is the long patent protection periods offered by the authorities, for having decided as a company to invest in R&D. The introduction of an orphan drug on the market involves a considerable amount of investment, so the FDA gives these drugs seven years of exclusivity from the approval date. This means that the orphan drug is protected for a long time, so there will be significant resources for the company and its investors to have exclusivity.

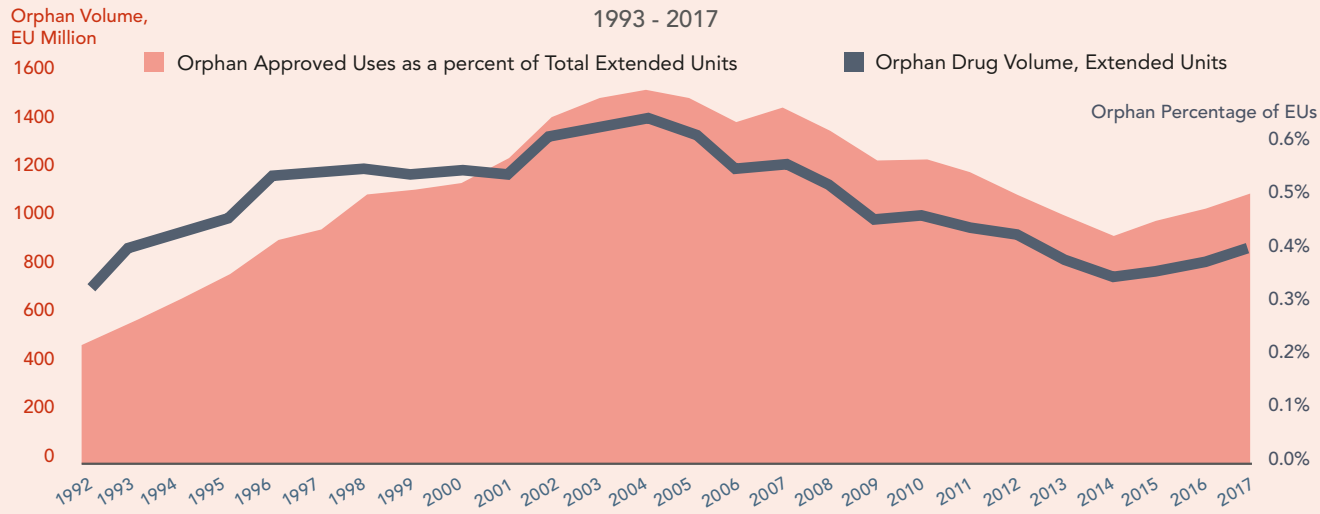
Additionally, orphan drugs often carry very high price tags because of their rare nature and lack of competition. Expect Washington legislators to make progress on this issue before 2020. Overall, I think there is some level of balance needed on investment required versus pricing that must drive economic sense in the equation. While increased orphan drug research has undoubtedly helped patients, there are downsides to this trend. Some economists and scientists suggest that companies have abused the financial incentives for rare-disease drug development, and they predict a coming backlash to the hefty price tags of these medications.

David H. Crean
managing director, Objective Capital Partners

> “PERHAPS ALL THESE BENEFITS GO TO REINFORCE WHY THE STOCK PRICES OF A COMPANY INCREASE BY 3.36 PERCENT AFTER THE ANNOUNCEMENT OF AN ORPHAN DRUG DESIGNATION”

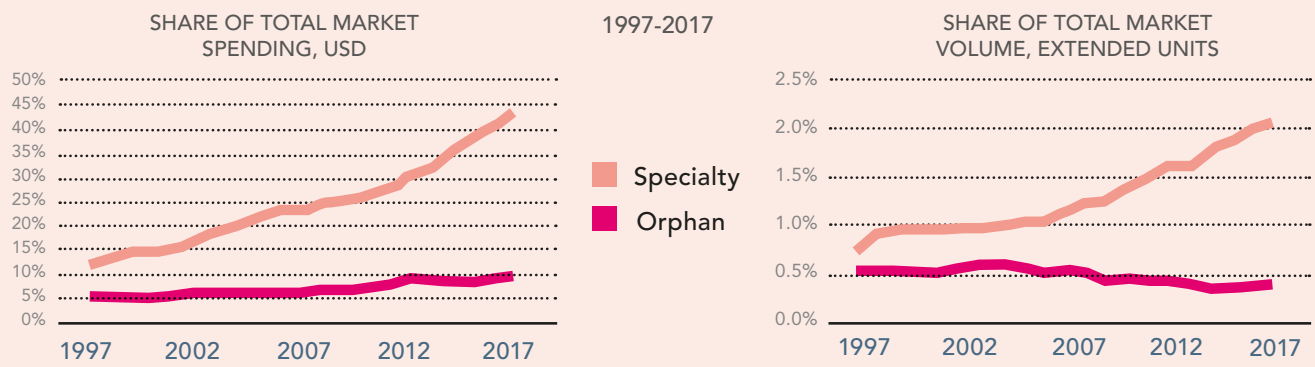
Lastly, an important factor to consider is the approval time, which is faster. This could be the biggest advantage of getting orphan drug status as companies and the FDA work hand in hand to bring these life-changing treatments to millions of patients. Perhaps all these benefits go to reinforce why the stock prices of a company increase by 3.36 percent after the announcement of an orphan drug designation, increasing the value of the company. Another study demonstrated that companies with orphan drug market authorization are more profitable and are more attractive investment opportunities than non-orphan drug companies.

ORPHAN DRUG VOLUME AND SHARE OF TOTAL DRUG VOLUME IN THE UNITED STATES



Source: IQVIA National Sales Perspective, Jan 2018; FDA Orphan Drugs @ FDA Database, accessed Sep 2018; IQVIA Institute, Sep 2018

SPECIALTY AND ORPHAN SHARES OF TOTAL SPENDING AND VOLUME



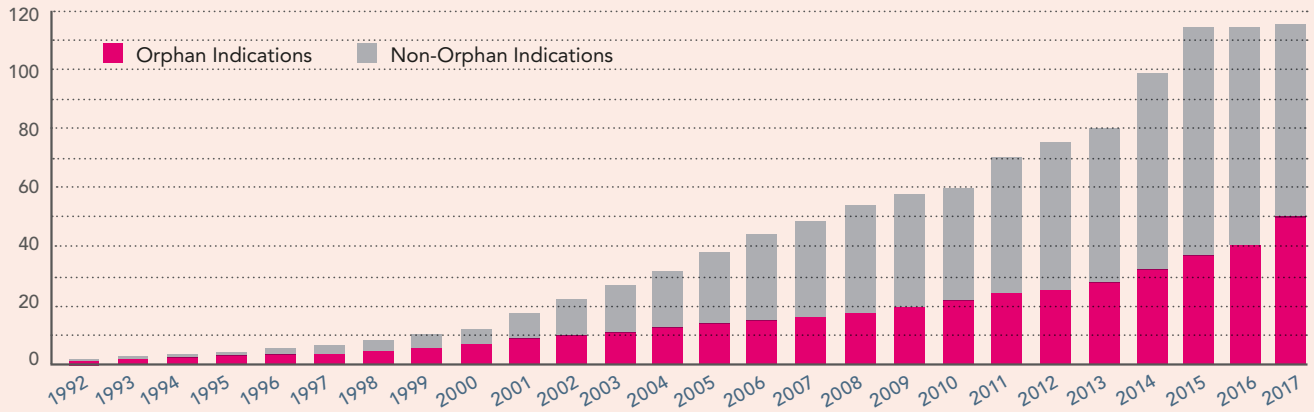
Source: IQVIA National Sales Perspectives, Jan 2018; FDA Orphan Drugs Database, accessed Sep 2018; IQVIA Insitute, Sep 2018

SPENDING ON ORPHAN DRUGS BY ORPHAN AND NON-ORPHAN INDICATIONS IN THE UNITED STATES

Source: IQVIA National Sales Perspectives, Jan 2018; FDA Orphan Drugs Database, Sep 2018; IQVIA Insitute Sep 2018

(1992-2017, USD Bn)

Note: The graphic represents sales of molecules with one or more orphan indications, split by sales of orphan indications and sales of non-orphan indications.



ACQUISITIONS CONTINUE APACE

Pharma multinationals' rush to snap up rare disease specialists continues with Ipsen's proposed acquisition of Clementia Pharmaceuticals. Industry insiders predict that this trend is set to continue well into the 2020s.

IPSEN BETTING BIG ON RARE DISEASE

Ipsen's USD 1.3 billion move to acquire Clementia – a Canadian biotech focused on bone diseases – will serve to boost the French firm's rare disease portfolio. Clementia hopes to gain regulatory approval for its potentially lucrative key product, palovarotene in 2020.

Ipsen CEO David Meek said of the deal, "The acquisition of Clementia Pharmaceuticals accelerates the ongoing transformation of Ipsen as we are successfully executing on our external innovation strategy to identify and acquire innovative medicines to serve patients with unmet medical needs."

Clementia CEO Clarissa Desjardins added, "Ipsen's global commercial presence and capabilities will expedite our shared vision of bringing palovarotene to patients around the world as quickly as possible. We anticipate a smooth transition of our operations into the Ipsen organization that will continue Clementia's vision of delivering palovarotene to patients worldwide."

For Ipsen, this deal represents a significant gamble on rare disease and the potential profitability of palovarotene; one it needs to pay off. Unless the company is willing to add significantly to the debt it is taking on to buy Clementia, the deal will account for the majority of its M&A firepower. That means the hunt for new assets to fuel growth may slow, leaving Ipsen reliant on palovarotene for inorganic growth.

ACTELION: FINDING UNMET NEED

The Ipsen-Clementia deal represents another milestone in a recent history of rare disease firms being snapped up by pharma multinationals, following on from Japanese firm Takeda's buyout of Shire and J&J's USD 30 billion acquisition of Swiss success story Actelion in 2017, a move that made global headlines thanks to its sheer scale.

Jane Griffiths, Actelion's global head, revealed the rationale behind the deal. She noted that, "With this type of deal, it's always important to select a disease area where unmet need remains; if there is no real room to improve on the therapy, then it might well be a struggle to create new value. In our case, Janssen gains an entire new franchise enabling it to deliver treatments across the entire continuum of care. Actelion products, meanwhile, benefit from being able to leverage the superior launch capacity and market reach of J&J. There is still a lot of scope for enhancement within the Actelion portfolio: namely new indications that still lie within the pulmonary hypertension (PH) and rare disease space."

Jane Griffiths
global head, Actelion

A NEW ERA FOR PATIENT ACCESS IN CANADA

Durhane Wong-Rieger, president & CEO of the Canadian Organization for Rare Disorders (CORD), explains the changing landscape for access to rare disease drugs in Canada and the actors involved in getting there.

Durhane Wong-Rieger
president & CEO, CORD

For anyone not paying close attention, you may have missed Health Canada's quiet release of an important webpage: "Canada's regulatory approach for rare disease drugs: orphan drugs." In 2017, when Health Canada unveiled its modernized Regulatory Review of Drugs and Devices (a.k.a. R2D2) and "pulled" the 2012 "draft" Canadian Orphan Drug Regulatory Framework, the rare disease community, including the Canadian Organization for Rare Disorders responded with initial disappointment and scepticism. I think we called it the "kiss of death."

So, why have we now become strong advocates for orphan drug review under R2D2? First, experience to date with orphan drug submissions to Health Canada has been very positive, including early clinical advice to review clinical trials with small patient populations to expedited pathways. Second, even though we lost the proposed option for aligned FDA/EMA/Health Canada "orphan designation", there is, in fact, considerable alignment of Health Canada with the US Food and Drug Administration and the European Medicines Agency (and other regulators) in terms of data sharing and work sharing. Third, Health Canada is offering aligned regulatory-health technology assessment reviews with the Canadian Agency for Drugs and Technologies in Health (CADTH) and l'Institut national d'excellence en santé et en services sociaux (INESSS) to expedite the process from regulatory approval to reimbursement recommendation.

This brings us to a major new reason for optimism for Canadian orphan drug access, despite previous pushbacks from our HTA agencies and the public drug programs. In October 2018, the provincial/territorial governments called for consultation on a newly

released "Supplemental Process for Complex/Specialized Drugs (including Drugs for Rare Diseases). To understand the significance of this announcement, one has to go back more than a dozen years, to 2006 when the Canadian governments created the first (and only) jointly funded program for one rare disease drug (actually two drugs for one disease, Fabry's Disease). At the same time, the governments committed to setting up an "expensive drugs for rare diseases" program, an initiative that vanished with a change in government.

> "SADLY, THE YIN (OPTIMISM) OFFERED BY THE PROPOSED EDRD SUPPLEMENTAL PROCESS IS CHALLENGED BY A SERIOUS YANG (NEGATIVISM), NAMELY THE PROPOSED FEDERAL REGULATORY CHANGES ANNOUNCED IN JUNE 2016

Fast forward to September 2014, following continuous advocacy from the patient community, the provincial health ministers (finally) created the Expensive Drugs for Rare Diseases Working Group (EDRD WG) with a mandate to explore the management of rare disease drug therapies with evidence-based approaches. That announcement was followed by four years of almost total "radio silence", punctuated by numerous individual, family and patient group protests over denied or delayed access to life-saving and life-enhancing drugs.

So, why is the proposed supplemental process creating a buzz among patients and prescribers? The "stated" primary objective is to implement a proactive, consistent, fair and transparent process ... for the purpose of making responsive funding decisions. As importantly, it recognizes the need for "modifications to the current national review process" for drugs based on criteria including disease severity, unmet needs, cost per patient, and disease prevalence. Drugs may be submitted concurrently to Health Canada, CADTH, the Patented Medicine Prices Review Board (PMPRB), and the pan-Canadian Pharmaceutical Alliance (pCPA) to reduce overall submission review time. In recognizing the limitations of clinical trial data, the WG proposes the collection and assessment of real-world evidence (RWE) to address the evidence gap and to inform continued funding, including potential changes in funding criteria, price changes or renegotiations, or delisting.

Interestingly, the proposed Supplemental Process reinforces the recommendations for a "managed access" process to rare disease drugs outlined in Canada's Rare Disease Strategy. This comprehensive strategy was released by CORD in May 2015 following a year of multi-stakeholder deliberations.

Sadly, the yin (optimism) offered by the proposed EDRD supplemental process is challenged by a serious yang (negativism), namely the proposed federal regulatory changes announced in June 2016. These changes will allow the PMPRB to impose arbitrary (not evidence-based) and draconian (up to 60 percent to 90 percent) price reductions on certain new and current prescription medicines, especially those for rare diseases. CORD is particularly concerned that potential PMPRB reforms will create powerful disincentives for rare disease drugs to be available in Canada, or at least, not until they have been successfully stabilized in terms of pricing and use in other jurisdictions.

Similarly, the government-funded pCPA, which negotiates the price of drugs paid by public drug plans, submitted a brief to the House of Commons' Standing Committee, which was conducting special hearings on "Barriers to Access Treatment and Drugs for Canadians Affected by Rare Diseases and Disorders." The pCPA, on behalf of the public drug plans, strongly endorsed the regulatory changes allowing for PMPRB strict price controls.

The irony of the government processes, which, on the one hand, could facilitate expedited access to necessary and promising DRDs and, on the other, allow prohibitive price controls that discourage entry of life-saving and life-enhancing therapies, including clinical trials and early submission.

Nevertheless, CORD, on behalf of the rare disease patient community, chooses to be optimistic, focusing on the opportunities and advocating vociferously against the barriers.

TOWARDS A NATIONAL STRATEGY

Bob McLay, vice president and general manager of Sobi in Canada, discusses the winding road towards a national rare disease strategy in Canada.

Rare disease drugs are different to other drugs. It often takes years for rare disease patients to find the right physician and determine a diagnosis. Even when a diagnosis is made, finding appropriate treatments can be laborious and the required drug might not be available or reimbursed.

Moreover, the distribution of rare disease treatments is often complex; they are not simply available in neighbourhood pharmacies, but often have to be obtained from a specialist and administered by injection, several times a day. There may also be a need for training around dietary restrictions and expensive patient support programs.

Furthermore, it is impossible to conduct large, randomized, placebo-controlled studies for rare diseases. Rare disease populations are small and often trials will be stopped early after a treatment effect is seen. Regulators and HTA bodies struggle to evaluate these products to the same level of accuracy as treatments for common diseases with more robust data.

Bob McLay
vice president and general manager, Sobi Canada

A rare disease pathway is crucial to be able to look at individual rare diseases differently and acknowledge the unique situations of various disease, treatment and research protocols. Governments across the world have implemented programs such as patent extensions, fee waivers and truncated review processes designed to incentivize companies to continue to invest in drugs for rare diseases and to get these drugs to patients.

In 2012, the former Canadian government issued statements that they were in the process of implementing a national rare disease strategy. Several years later there is still no legislation in place. Health Canada representatives recently acknowledged that a new regulation system was planned. Although this is encouraging, nothing concrete has come of it yet. The initiation of a study on how to implement a national pharmacare program may represent an opportunity to finally have the rare disease community acknowledged and cared for more effectively.

It is essential for Canada to move forward with a rare disease strategy. We tend to rely on innovation from other countries' research, leaving Canadian patients hoping that innovation comes to Canada. With a tough regulatory and reimbursement system not designed to accommodate rare disease drugs, often innovation either does not come or is severely delayed. Without a predictable rare disease framework and reliable funding model, innovation and investment will slow down or cease altogether.

Only 60 percent of rare disease drugs make it to the Canadian market and approval takes six years longer than in Europe or the USA. Despite being an advanced industrialised country, Canada has some catching-up to do to be at least on par with other countries of our size and economy.

THE ULTRA-RARE SPECIALIST

Alexion targets patient populations of less than 20 patients per million. Christophe Bourdon, SVP EMEA, discusses the company's progress towards developing access for patients across the region.

What is Alexion's mission?

CHRISTOPHE BOURDON (CB): Alexion is unique in our commitment to developing and delivering transformative treatments for life-threatening ultra-rare diseases where no therapeutic alternative exists for patients.

To put this into perspective, out of a patient population of one million, about 50,000 people would have a condition like diabetes; less than 500 would have a rare disease; and less than 20 patients would have an ultra-rare disease. And the ultra-rare diseases we treat impact even fewer patients than this.

As well as developing transformative treatments for ultra-rare diseases, our aim is to engage with regulators, payers, and healthcare providers to ensure our treatments are available to the patients who need them. It is also crucial to have our dedicated teams on the ground to educate physicians about these diseases, and implementing diagnostic initiatives to help ensure that patients receive an accurate and rapid diagnosis.

What role has the EMEA region, and Switzerland in particular, played in Alexion's mission?

CB: Key research centres and hospitals across the EMEA region have played a critical role in Alexion's R&D programs, and we also have our own R&D centre in Paris, which we opened two years ago. In Switzerland specifically, the medical research centres and network is renowned, and we have recently partnered with the University of Zurich to create a fellowship in bioinformatics specialized in rare diseases. We are very proud to have just enrolled the first fellow into the program.

High-cost medicines draw political and media attention, and as they target ultra-rare diseases, Alexion's products are all high-cost per patient medications. Given this scrutiny, what is your strategy for engaging payers?

CB: Alexion is one of the very few biotech companies focusing on patients with extremely rare diseases. These patients are often forgotten, and they and their families suffer with little hope. As an innovator, Alexion has focused on delivering life-changing treatments to these patients who do not have any alternative.

When we engage with payers, the first thing we discuss is how severe and debilitating these diseases are – how it is a matter of life or death. We discuss the transformative benefits our products bring to patients – for example, how with a treatment option like Strensiq, babies can survive past the first year of life and go on to live more or less normal lives. Finally, we emphasize just how rare these diseases are; particularly in comparison to other conditions which themselves are considered rare. This is what payers recognize; the devastating nature of the disease, the rarity and the associated challenges of that rarity, and how life-changing the benefits of our treatments are.

RECONSIDERING APPRAISAL APPROACHES IN THE UK

Sobi's UK and Republic of Ireland general manager Neil Dugdale outlines how the UK's public health system should reconsider its approach to appraising rare disease treatments.

Within NICE [the UK's HTA body], there is a 'one-size–fits-all' approach to treatment appraisal, as it was designed to analyse the cost-effectiveness of products treating thousands of patients. In rare diseases, however, we see patients gaining access to treatments – treatments that could either cure or extend their life substantially with a good quality of life – significantly later than in most other developed economies.

The issue is not limited to rare diseases: one reason the Cancer Drug Fund was established was to get innovative oncology medicines to patients faster because the NICE model did not work. In rare diseases we have to consider unique numbers: there are approximately 8,000 rare diseases, and only around 400 treatments available. With pharmaceutical companies now considering not launching new products in the UK, this number of treatments is not likely to rise significantly in the future, potentially leaving some patients without access to life-changing new treatments.

There is now a special reimbursement pathway for treatment of rare diseases in the UK – the NICE highly specialised technology (HST) process. But even if you pass the first steps of the process and are recognised as cost-effective by NICE, if your product is to cost more than GBP 20 million over three years you are forced to pause the process to then engage in additional reimbursement negotiations with NHS England. This is often the case with rare disease drugs that will only be used to treat small numbers of patients but still have the substantial research costs of other drugs with no extra patent protection.

In rare diseases, patients have to wait an average of five years to get a diagnosis and many of these patients are children. These families with sick children have been stressed and traumatised for an average of five years. Some are then told that there is either no diagnosis or that there is a diagnosis but that no treatment exists. The best case is diagnosis and treatment. However, with the current appraisal process, the treatment might be delayed significantly compared to other developed economies; my fear is that some may never reach the market if an agreement cannot be reached with the NHS. Furthermore, a company may decide to prioritise supply to countries that don't insist on the low prices demanded by the NHS. The UK is a tough market and it is getting tougher. The situation where a family has to go through the extreme stress of non-diagnosis, to the relief of a diagnosis and a suitable existing treatment, to then learn that it is not yet available in the UK, is just not acceptable for a top five global economy, considering its science base and global leadership.

Neil Dugdale
general manager, Sobi UK

GOING GLOBAL

Formed in 2015, listed UK start-up Amryt targets rare diseases with high unmet medical need. With one commercial asset on the market, a strong pipeline of development assets and a commercial infrastructure across the EMEA region already in place, the company is aiming to expand rapidly.

Joe Wiley
CEO, Amryt

Rare diseases affect 350 million patients globally and, as Amryt's CEO Joe Wiley points out, "there are around 7,000 identified orphan diseases, but only some 500 or so approved drugs to treat them." He continues, "There is a long way still to go to develop drugs for all these indications. Therefore, regulatory incentives for companies like us to develop products for rare diseases are increasingly common and investment is encouraged."

Amryt's strategy revolves around gaining market access and reimbursement for these rare disease treatments. Wiley explains, "For the first time, patients have access to Lojuxta [Amryt's lead commercial asset – Ed.] in England through the NHS, while we also expect reimbursement announcements in other countries soon. In addition, we have also been highly successful in bringing together highly talented people: we assembled a strong commercial team and managed to ramp up our know-how in market access across Europe. It's a complex environment to navigate, but we have been successful despite the fledgling size of the company."

Looking globally, Wiley notes that "Amryt has already built a commercial infrastructure in Europe and the Middle East, which we can leverage. The first milestone was to become a commercial stage business through building our sales infrastructure and a distributor network. This should provide a powerful foundation from which to launch our future growth." He continues, "We generally access patients through key opinion leaders and, with that in mind, have been attentive to crafting a network of experts and opinion shapers across the globe. We have expanded our business recently in the Middle East and we identified lots of KOLs and a hospital in Saudi Arabia that attends to more patients than have been diagnosed in the whole of the UK. Therefore, the Middle East will be a really important future driver of our business."

Amryt can also lean on the expertise of Harry Stratford, the founder of Shire Pharmaceuticals, to guide their growth strategy. Wiley exclaims, "We are delighted to have Harry as our chairman. Having his experience is fantastic as he is a veteran of the pharmaceutical industry and a highly successful serial entrepreneur. I believe he sees in our team parallels to what he did when he developed his businesses. Our strategy is to acquire, develop and commercialize; this is where we are aligned with Harry as it was the pathway that Shire followed in its inception."

> "AMRYT HAS ALREADY BUILT A COMMERCIAL INFRASTRUCTURE IN EUROPE AND THE MIDDLE EAST, WHICH WE CAN LEVERAGE"

ORPHAN DRUG ACCESSIBILITY & SOCIAL MEDICAL COVERAGE IN CHINA

Kevin Rufang Huang, president and founder of the Chinese Organization for Rare Disorders (CORD), breaks down the status quo of rare diseases and orphan drug access in China.

The official "First List of Rare Diseases" was released in China in May 2018. 121 rare diseases are included in the list. It is a huge milestone in the development history of China's rare diseases, signifying the Chinese government's determination to address the accessibility of rare disease drugs.

Currently, in China, more than 3 million patients suffering from one of these 121 rare diseases are still facing mounting challenges: difficulty in obtaining clear diagnoses; lack of treatment options; and the limited number of available orphan drugs in China. Even for those drugs available in China, sourcing can still be a problem and many carry prices so high that they are totally out of reach for most patients without social medical coverage. Inaccessibility and unaffordability are the two biggest obstacles for patients, as a result, more than 50 percent of the rare disease patient population in China did not receive timely and adequate treatments.

By December 2018, 74 rare diseases in the "First List of Rare Diseases" are considered "curable". 162 drugs for these 74 rare diseases have been approved in the US, the EU or Japan, while 83 drugs (51 percent) for 53 diseases are approved in China. However, just 55 drugs for 31 rare diseases get definite indication registration in China, and just 29 drugs for 18 rare diseases are covered under the National Medical Insurance, Employment Injury Insurance and Maternity Insurance.

WAITING FOR CHINESE APPROVAL

There are tremendous obstacles in bringing an orphan drug to China. Drug companies are often resigned to inaction in an uncertain market. Uncertainties around obtaining market approvals (regulatory hurdles) and subsequent drug sales (income uncertainties due to a small patient population and lack of social medical coverage), and the potential moral and ethical scrutiny cause further dilemma for companies. As a result, most companies choose to "wait and see".

Lack of orphan drug designation and a separate approval path for orphan drugs pose an invisible wall for drugs to enter the Chinese market. More favourable policies and regulations are needed to encourage orphan drugs to enter China and to obtain registration and market-approvals.

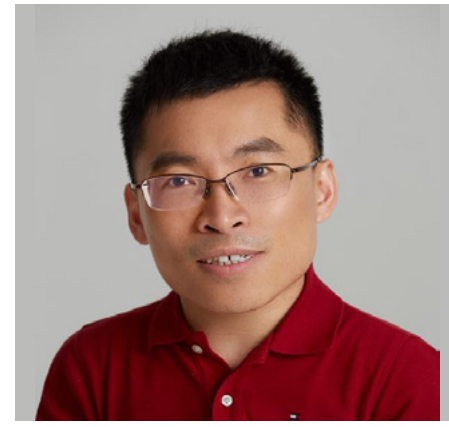
Although some rare diseases have treatment drugs available in China, they are not specifically designated for such diseases. In comparison to already approved orphan drugs in other markets, the drugs used here in China are secondary or tertiary treatment options with lesser efficacies, leading to less desirable outcomes for patients and their qualities of life.

ALTERNATIVE INDICATIONS

There are a group of 20 drugs approved in China for other indications. They could be used to treat the 22 rare diseases in the "First List of Rare Diseases". But they are not approved specifically with these rare disease indications, thus in principle should not be used to treat them.

With limited availability of drugs, doctors and researchers are forced to experiment with various prescribing options: off-label, using old drugs for new indications, or even "prescribe to trial" etc.

In order to control off-label usages and avoid drug abuse, most doctors advocate that the prescribing authorization is limited to a few experienced clinicians. This prescribing privilege to a special few, however, also leads to vastly different treatment qualities, causing patients to receive differentiated, incoherent treatment across different regions.



Kevin Rufang Huang
president and founder, CORD

HIGH PRICES

Getting the prescription is just the first step towards treatment. There is a reverse correlation between the size of the patient population and the cost of the treatment: the smaller the population, the higher the price is likely to be. Many orphan drugs carry sky-high prices. Without the support of social medical insurance, most patients cannot afford them.

The Chinese government has made good progress on social medical coverage for rare diseases. Among the 55 orphan drugs approved in China, 29 for 18 rare diseases are on the National Health Insurance List, 9 of which for 11 rare diseases are on the Category I Reimbursement scheme, meaning no out-of-pocket payment for patients.

There are still 26 drugs for 21 rare diseases that have not been covered under the social medical insurance. 13 of these 21 don't have drugs under coverage, which means patients must bear all medical costs on their own. The estimated number of patients for these 13 diseases is around 230,000 in China. Most patients need lifelong treatment. 11 drugs for these 13 diseases cost more than 80,000 yuan per year. Without medical insurance, it is very difficult for patients to afford the full treatments they need.

"THE LAST MILE" FOR ORPHAN DRUGS ACCESS IN CHINA

Even after an orphan drug is approved and listed on the national social insurance list, challenges remain. Between patients and their drugs lie many obstacles. Mainly:

1. Hospital procurement restrictions:

Orphan drugs, which carry high costs but low demands in comparison to other drugs, pose great challenges to the management of hospital pharmacies.

2. Physician prescription restrictions:

Pressured to keep the desired ratio of drug costs vs. the total insured cost, doctors are constrained to prescribe the orphan drugs to the patients, thus making reimbursement nearly irrelevant.

3. Restrictions on outpatient reimbursement:

There are vast regional differences in reimbursement policies on outpatient costs and costs on chronic and severe diseases. There are many different rules and regulations from different regions in terms of deductibles, co-pay ratios, and max out amounts.

4. Obstacles caused by a less-than-ideal referral system:

It is difficult for patients in a non-provincial capital to maintain long-term treatment. They can only choose low-dose treatment, self-medication, or even giving up treatment altogether. Treatment compliance is difficult to reinforce.

5. Drug deprivation crisis:

There are often inadequate supplies of low-cost drugs, manufacturers are sometimes forced to shut down manufacturing, leaving patients with no treatment options.

Underlying all the problems mentioned above is the insufficient coverage of social medical insurance on rare diseases; and the high prices of orphan drugs.

While the orphan drug accessibility issue poses significant challenges to China's healthcare reform, it also presents an opportunity. Improving the accessibility of orphan drugs and expanding social medical coverage on rare diseases will provide a breakpoint for healthcare reform. It might also help explore ways to elevate China's rare disease initiatives, promote innovation and make a contribution to the rare disease space worldwide.

Sobi launched Liberate Life on World Haemophilia Day, a vision of life beyond haemophilia. In a series of long-term commitments, Sobi seeks to shape new standards, optimise treatment, build evidence, create sustainable access and provide community support in haemophilia care.

Haemophilia is a rare inherited bleeding disorder, in which the blood does not clot properly, taking longer than normal for the bleeding to stop.[1] This can severely impact a person's quality of life both physically, such as a reduction in mobility due to recurrent joint bleeds[2], which can limit a person's daily activities,[3] and psychologically, having a negative impact on their mental wellbeing.[4]

Despite recent advancements in treatment, people living with Haemophilia often make compromises in their everyday lives. This insight, among others, stems from a large-scale, pan-European ethnographic study of the lives of people living with Haemophilia undertaken by Sobi in the summer of 2018.[5] The in-depth research exposed the challenges, aspirations and unmet needs, behaviours and perceptions related to life with Haemophilia, inspiring the creation of the Liberate Life vision.

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