FT Health

Combating Rare Diseases

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Genomic advance lifts patients' hopes

Personalised treatments are in prospect, as study of mutations creates more targeted therapies, reports *Andrew Ward*

For decades, rare diseases were all but ignored by the pharmaceuticals industry. The science was difficult and the economics even harder.

So it is testament to how much has changed that today, rare diseases — defined in Europe as a condition affecting fewer than 1 in 2,000 people — are among the hottest areas of drug development.

A third of all medicines approved by the US Food and Drug Administration in the past five years have been for rare diseases — including a record 17 in 2014.

Peter Saltonstall, president of the US patient group National Organization for Rare Disorders (Nord), says all the signs point to this momentum continuing. "We're in a very exciting period of scientific and technological innovation."

This rush of R&D is delivering fresh growth to the pharmaceuticals industry — and raising new hope for patients previously stranded on the margins of medical science.

While each is rare in its own right, the roughly 7,000 diseases that fall under the category collectively represent a formidable challenge. About 350m people globally have some kind of rare disorder — 10 times the number living with HIV.

Focus: rush of R&D offers encouragement for sufferers previously stranded on margins of medical science — Phanie/Alamy

They range from relatively well-known ailments such as cystic fibrosis and multiple myeloma to obscure ultra-rare conditions, including perinatal hypophosphatasia and dopamine-responsive dystonia. Less than 10 per cent have an effective treatment.

This high unmet need has combined with three big trends to attract a surge of investment in rare disease R&D.

First, and most important, are the scientific advances that have sprung from the decoding of the human genome a decade ago. This has made it possible to develop more personalised medicines targeted at specific genetic mutations.

Such an approach has proved especially fruitful against rare diseases, because about 80 per cent of them are genetic in origin. To take one example, Kalydeco, made by US-based Vertex, targets various mutant genes associated with certain types of cystic fibrosis.

"The genomics revolution has allowed us to understand rare diseases on a molecular level in a way that was not possible before," says Jimmy Lin, founder of the Rare Genomics Institute, a US non-profit research network.

These breakthroughs have been accompanied by a second driving force: digital technology. The ability to harvest and analyse large volumes of genomic data are accelerating the hunt for genetic markers of disease and, crucially, helping identify people with rare conditions who might previously have gone years without diagnosis.

In the UK, for example, the government-backed 100,000 Genomes Project is building a database of DNA codes from patients with rare diseases and cancers — and their relatives — to aid diagnosis and research.

Technology is also helping small, far-flung patient communities support the push for new treatments. Before the internet, their best hope of wider attention was for a doctor to write about their condition in a medical journal. Today, social media gives them a platform to share information and lobby drug companies and regulators for action.

Yet none of these scientific or technological advances would have turned the tide without the third trend: a shift in the pharma business model away from one-size-fits-all "blockbusters" and towards high-priced niche treatments.

Continued on page 2

Inside

Patient lobby groups can be a catalyst for new therapies

Advocacy

Community support bodies are a powerful force behind funding, research and drug approval, says *Sarah Murray*

It was after learning that their son Hawken, now aged 18, had Duchenne muscular dystrophy, a childhood disease causing progressive muscle weakness, that Debra and Paul Miller decided to establish CureDuchenne, now a leading California-based advocacy group.

But while some families have the necessary skills and financial resources to do this, forming a support group puts many on to a steep learning curve.

"There's everything from the mom and pop who just got the diagnosis, to a body that's grown to a point where it's funding the research and writing the guidance for the FDA [the US Food and Drug Administration]," says Peter Saltonstall, president and chief executive of the US's National Organization for Rare Disorders (Nord).

Once established, patient advocacy groups help families support each other, and many go on to become powerful forces, funding research and pushing for drug approvals.

For the Millers, a background in the private sector helped them as they built up their group. "In our case, it worked in our favour that we didn't know much about non-profits," says Ms Miller. "We ended up running [this] like a business and held ourselves accountable, to show success against our stated mission."

But she stresses that, while the bureaucratic procedures for setting up a non-profit are relatively simple, there is much to learn. "You file your paperwork and set up a website and you can be in business," she says. "But it's a far cry between setting one up and being successful in your mission."

For families that have decided to set up an organisation, various forms of support exist. In the US, Nord acts as an incubator, offering training, mentoring and advice on everything from creating a scientific advisory board and establishing a fundraising strategy, to building a website. "Nord is a marketplace for help," says Mr Saltonstall.

'You file your paperwork and set up a website and you can be in business' **Debra Miller**

However, Ms Miller argues that the first task for families is to do some research to find out whether or not they should set up an advocacy group. "If you can find another organisation that has a common goal, don't," she says. "There's always a cost involved and the more you can combine your efforts, the better."

Collaboration is a principle also emphasised by Charles Mohan, chief executive and executive director of the US-based United Mitochondrial Disease Foundation.

"We use three main directives — co-ordination, communication and collaboration," he says. "We want to co-ordinate all efforts to see who's doing what out there."

One of the most difficult things for groups is approaching government. For this reason, Nord also works with its members to help them, for example, by providing analyses of legislative and regulatory activity.

Another challenge facing those engaged in rare disease lobbying is making their voices heard. "When people go to talk to legislators, they fail to realise they're not the only ones," says Mr Mohan, who is also co-chair of the Coalition of Patient Advocacy Groups, part of the Rare Diseases Clinical Research Network. "They may be one of a hundred people that office sees in a day."

This, he says, means identifying the best channels to go through and conveying the information in a compelling way, with messages that are fresh and reports highlighting the latest research. It also demands staying power. "You need to keep coming back," says Mr Mohan.

As better genomics uncover further diseases that are gene-specific, the number of patient advocacy groups is growing rapidly.

Mr Saltonstall cites the case of Duchenne muscular dystrophy: "There are about 40 groups out there, with every one working on a gene and focusing on the segment of their disease. We are going to see more and more of that."

This trend increases competition for "airtime" with politicians, he notes, which is another reason groups must become more collaborative. "We're trying to help patient groups understand that a single voice has more power."

Significant, too, is the role that groups can play in generating funding for R&D, particularly for small biotech companies that need to take the next step.

For example, CureDuchenne supports research through its company CureDuchenne Ventures. This month, the company invested $1m in California-based Myotherix, a US biotech company, to support the pre-clinical studies needed to develop new therapeutics for treating Duchenne and other muscular dystrophies.

"Patient advocacy groups are a necessary catalyst for further research — and it's fuelled by their passion," says Mr Mohan. "That passion is what will get them the financial resources they need, to support the research."

Niche treatments become big business

Orphan drugs

Investors are drawn to the low-volume, high-margin model, writes *David Crow*

Orphan drugs might target small groups of patients, but they are increasingly big business.

Pharmaceutical companies, from tiny biotech start-ups to Shire, the London-listed group with a market capitalisation of more than £30bn, are focusing on drugs for orphan diseases, lured by regulatory incentives and a low-volume, high-margin business model.

Ever since the introduction of the US Orphan Drug Act 32 years ago, developing medicines for rare disease has become the so-called "Goldilocks option" for some pharma companies.

Groups selling orphan drugs are granted seven years of market exclusivity (against five years for most medicines), along with generous tax credits. Because they target diseases that do not already have treatments, they also tend to benefit from other regulatory initiatives designed to get drugs to market more quickly.

Once approved, the drugs often have a ready-made audience: many patients with rare diseases are well organised in advocacy groups, have been waiting for years for a treatment, and are primed to request the medicine from their doctors once it is available.

Global sales of orphan drugs are expected to jump as more companies enter this field, rising by 11 per cent each year to reach $176bn in 2020, according to EvaluatePharma, the research group.

Investors have taken notice. In the past year, the value of US biotech companies focused on rare diseases has risen by about 56 per cent, according to the Orphan Disease Index, assembled by JMP Securities, a San Francisco investment bank.

That performance was even better than the broader Nasdaq biotech index, which is up by roughly 37 per cent over the same period, and smashed the S&P 500 index, which is 5 per cent higher.

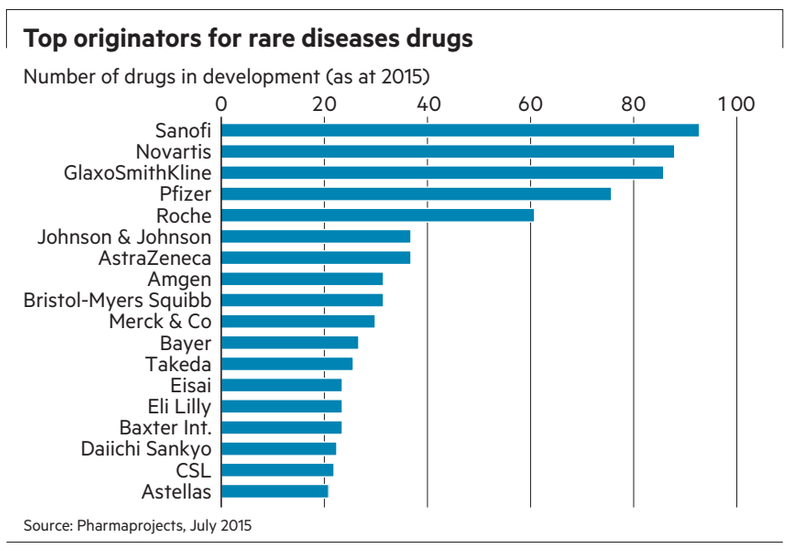
Venture capitalists who invest in early-stage companies have also increased their bets in the US. In 2012-14, these early-stage companies raised more than $500m each year, compared with 2008 when they pulled in less than $200m.

Incentive: groups selling orphan drugs are granted seven years of market exclusivity and generous tax credits — Bruce Ando

Orphan medicines account for about one in three drug approvals in the US but no one in the industry expects the proliferation of medicines to end in the near future, according to Christopher Milne, an orphan drug specialist at the Tufts Center for the Study of Drug Development. "There is a lot of low-hanging fruit," says Mr Milne. "With 7,000 rare diseases, there is plenty of potential, because just 10 per cent of those have treatments."

The opportunity has prompted Shire to try to build an orphan drugs powerhouse as it seeks to reduce its overall reliance on Vyvanse, its blockbuster treatment for attention deficit hyperactivity disorder.

To that end, it recently bought NPS, a US-based rare disease specialist, for $5.2bn and is in the throes of a $30bn hostile takeover attempt of Baxalta, another US group, which focuses on rare blood disorders.



Rare diseases is one of the few areas in pharmaceuticals where it is not essential to be big. Many successful smaller biotechs will have to decide whether they can go it alone. Those lucky enough to win approval can struggle to build a global sales force and manufacturing capabilities, forcing them to turn to big pharma.

To get their medicine to market, they often have to sell the company outright to a larger group or strike a sales and distribution partnership in exchange for a large share of revenues and profits.

Companies focused on orphan drugs, however, are less likely to be forced into the same choice: because the patient populations are so small, they can afford to make and sell the drug themselves.

Alexion, founded in 1992, is a case in point. By switching its focus to rare diseases 10 years ago, it has been able to build its business without selling itself to, or joining forces with, a larger rival.

Its only approved product in the US is Soliris, a treatment for paroxysmal nocturnal haemoglobinuria, an ultra-rare and deadly blood disorder.

The drug is also used to treat atypical haemolytic uremic syndrome, which causes blood clots in small blood vessels throughout the body.

Alexion's market capitalisation is almost $43bn. Despite booking sales of $2.2bn in 2014, it employs just 2,800 people, equating to revenue of almost $790,000 per employee, one of the highest ratios in the industry.

But companies such as Alexion can experience growing pains, too. Once they have developed a successful orphan drug and sold it to what is always a small patient population, it can often be hard to create growth.

Alexion tackled that problem this year by buying Synageva, another rare diseases group, for $8.4bn, a 139 per cent premium on its market value before the deal was announced. It was among the biggest premiums ever paid for a company, according to Dealogic.

In a recent note, Geoff Porges, an analyst at Bernstein, explained that Alexion had to pay such a high price because companies developing orphan drugs are, by their very nature, quite rare.

"Synageva was one of a handful of rare disease companies with real scale," said Mr Porges.

"We believe the other biotechs focused on rare diseases that Alexion reviewed were relatively few in number and had idiosyncratic drawbacks."

Either the companies had proven assets, in which case they commanded very high valuations, or they were early-stage biotechs with risky, experimental drugs, Mr Porges added.

Genomic advance lifts patients' hopes

Continued from page 1

For decades, the holy grail for pharmaceuticals companies was finding drugs for common conditions, where the large number of patients guaranteed multi-billion-dollar revenues. But a wave of patent expiries has forced the industry to look elsewhere for new drugs.

Regulators have encouraged the shift by creating incentives for companies to focus on so-called "orphan diseases" that lack an effective treatment — a category that includes most rare diseases.

Fast-track approval processes have been introduced in the US and Europe to accelerate the path to market. This has made rare diseases increasingly attractive to developers, compared with the slow and costly large-scale clinical trials required of mainstream drugs.

But perhaps the biggest commercial appeal is the high prices and margins commanded by rare disease therapies.

Traditional blockbusters involve heavy expenditure and armies of sales reps competing against rival products, while rare disease medicines are typically the only product for their condition, and can be sold with minimal overheads via a few specialist medics. Companies justify high prices by the small number of patients from which to recoup costs — and the big medical benefit they often provide to patients.

Alexion, a US-based rare disease specialist, for example, charges more than $400,000 per person per year for Soliris, a medicine for a kidney condition called atypical haemolytic-uremic syndrome. This allowed the company to generate $2.2bn of sales last year from its sole approved product, serving a total market of just a few hundred patients.

Returns such as these are attracting increasing interest from big pharma groups. In April, Bristol-Myers Squibb of the US agreed a partnership worth up to $1bn with a small Dutch company called UniQure, whose treatment for lipoprotein lipase deficiency has been dubbed the world's most expensive therapy, at €780,000 a patient.

Companies are confident that sky-

Paucity proves the mother of experimentation

Clinical trials

Small patient numbers pose big problems in researching therapies for rare conditions, reports *Andrew Ward*

Clinical trials are the most expensive part of drug development: a big late-stage study can cost hundreds of millions of dollars and take many years.

It is easy to see the appeal, therefore, of rare disease trials involving a few dozen people, compared with the hundreds or sometimes thousands required to prove the safety and efficacy of more mainstream therapies.

However, using a small number of patients also brings challenges. It can be difficult to find enough of them to produce statistically significant data, particularly when drugs are targeted at a subset of a tiny population.

Take, for example, Kalydeco — a much-heralded breakthrough against cystic fibrosis from Vertex of the US. It works only for those with a particular genetic mutation, which accounts for just 4 per cent of the 30,000 people in the US with the disease. Other conditions are even rarer.

If it can be hard to find patients, finding expert doctors to oversee trials can be harder still. While there is rarely a shortage of specialists for cancer or heart disease trials, with rare conditions there may be only a handful of experts.

"Finding the lead investigator — the top world expert — is critical as around them will be a network of doctors and patients," says Neil Clark, chief financial officer of Ergomed, a UK-based company which manages trials for drug groups.

Companies will often carry out trials for more common conditions in regions such as eastern Europe to limit costs, but there is rarely the luxury of such a choice with rare diseases.

"You have to go where the patients and the experts are," says Mr Clark. That usually means the US and larger western European countries.

Patients often have to be transported long distances — sometimes across borders — to attend research centres. Although absolute costs are lower, the cost per patient of clinical development is 25 times higher than for more common conditions, according to Hartmann Wellhoefer, head of medical affairs for rare diseases at Dublin-based Shire. "A lot of support is needed for each investigator and patient."

Phil Vickers, Shire's head of R&D, says there is room for greater co-operation between US and European regulators.

For example, the term "orphan disease" — used to describe rare and untreatable conditions — is defined differently on either side of the Atlantic. And the US Food and Drug Administration and the European Medicines Agency sometimes have different requirements for clinical trials.

"Then you need two sets of patients and it becomes even more difficult," says Mr Vickers.

Measuring the benefit of a drug can be fiendishly tricky when the disease is not fully understood and there has been no prior treatment, he adds. "Usually, there is no standard of care. That is very different from diseases where the pathway is well trodden."

The first step is often what researchers call a "natural history study" of patients to gain a better understanding of how a disease manifests itself and progresses. This can help establish what biomarkers (indicators of disease) should be measured in trials, and what the "clinical end point" should be that determines success or failure.

Drug companies routinely work closely with patient groups, expert doctors and regulators while designing their trials to make sure the right medical questions are asked.

There is also likely to be early consultation with health economists and "payers" — the health services and insurers who buy drugs — to agree what evidence is needed to confirm value for money.

"It's not just what value we can bring to the patients, but what value we can bring to society," Mr Vickers says.

Tight limit: Kalydeco targets rare mutation of cystic fibrosis

"If we can get patients out of intensive care earlier or reduce hospitalisation in the long run, what savings does that bring to payers?"

Such questions are becoming more pressing amid political scrutiny of the exceptionally high price of rare disease drugs, which can cost several hundred thousand dollars per patient per year.

These challenges — low numbers, uncharted science and high costs — are encouraging drug companies, regulators and payers to experiment with new ways of evaluation.

Increasingly, conditional approvals are being granted after successful early-stage trials with the proviso that further data be collected to demonstrate "real-world" efficacy.

"We are creating new pathways," says Mr Vickers. "That's what makes [working in] rare diseases so exciting, but also challenging."

7,000
The number of diseases that fall under the category of 'rare'

350m
Number of people globally that have some kind of rare disorder

high prices will be tolerable for health systems, because so few patients require treatment. However, as more drugs arrive, the collective burden is rising.

They have achieved very high pricing while they have been a tiny proportion of the drugs bill, says Glyn Edwards, chief executive of Summit Therapeutics, a UK company developing a therapy for Duchenne muscular dystrophy. "But there is doubt about whether these prices are sustainable."

Fraught policy debates are under way in cash-strapped European health systems over how much public spending on rare diseases can be justified.

Prevention and treatment of common conditions produce a larger collective benefit to society, but the principles of universal healthcare demand that people with unusual diseases should not be abandoned.

Patient advocates such as Mr Saltonstall insist that the benefits of rare disease drugs will outweigh the costs. He says they are the leading edge of a wider shift towards personalised medicine that will eventually make health systems more efficient.

"In the long run," he says, "every disease will be rare."

High prices force payers to find ways to cut their bills

Incentives Health providers are joining forces in an attempt to negotiate discounts, says *David Crow*

Scrutiny: insurers keep close watch on prescription of orphan drugs — Dreamstime

Nothing strikes fear into pharmaceutical executives so much as pricing.

Those who pay for healthcare — whether the insurance companies in the US or the public health systems in other countries — have warned they cannot cope with rampant drug price inflation at a time when society is ageing.

Yet there is one area that has proven relatively sheltered from pricing pressure: orphan drugs for rare diseases.

This is all the more surprising, given that these drugs normally command very high prices.

Soliris, a drug made by Alexion Pharmaceuticals to treat two rare diseases, costs between $400,000 and $560,000 per patient per year, for instance.

An Alexion representative says it has experienced little difficulty getting the drug on to US "formularies" — the lists of approved drugs compiled by the pharmacy benefit managers (PBMs) who buy medications.

The rationale for charging such high prices is that orphan drugs, by their very nature, will only ever be prescribed to a small number of patients.

If a pharmaceutical company is to recoup the investment it takes to develop a new medicine and have it approved, it must charge more per head for orphan drugs than traditional ones.

In a recent report, Express Scripts (the largest of the PBMs) used this argument to justify its decision to take on another company, Gilead, which charges $1,000 a pill for a drug that treats hepatitis C, a common illness.

"Orphan drugs are among the most expensive medications in the US, often costing tens of thousands of dollars per prescription," the report said. "[They] treat extremely rare conditions . . . typically only several thousand patients or fewer. The high price tag is necessary — and justified — to fund manufacturer research and development costs."

However, orphan drugs are not entirely immune from pricing pressure. In an article published in the Journal of the American Medical Association last year, researchers found that many insurers were demanding that doctors get explicit permission before prescribing orphan drugs, or requiring that patients undergo a clinical diagnostic test to ensure they have the relevant condition.

Analysts at Wells Fargo bank think PBMs will continue to support the makers of orphan drugs, because, while they cost more per head, these companies tend to evaluate medicines on the "pooled" price rather than an individual basis.

They also reckon that PBMs do not want to contend with the negative publicity of denying someone with a rare, quite often deadly condition a potentially life-saving drug. "The political risks of denying reimbursement or coverage may outweigh any potential cost-savings," the Wells Fargo analysts wrote in a recent note for investors.

Some policymakers know those risks all too well. Two years ago, the Belgian health ministry found itself at the centre of a row over its refusal to pay for Soliris for a seven-year-old boy suffering from a rare kidney disease. It eventually agreed to foot the bill after negotiating a discount from Alexion. The case suggests that, while Alexion might be able to set high prices in its domestic market, it could face pressure from health systems in other countries.

This year, Belgium formed a partnership with the Netherlands to purchase orphan drugs jointly in an attempt to extract discounts from manufacturers.

Canada, too, exerted pressure in February when one of its regulators launched a hearing to review what it described as "excessive" pricing for Soliris.

With orphan drugs accounting for roughly a third of all new medicine approvals in the US, says Christopher Milne, an orphan drug specialist at the Tufts Center for the Study of Drug Development, it is an open question as to how long rare disease drugmakers would be able to withstand pricing pressure in the world's largest and most lucrative healthcare market.

But currently there is little sign of a crackdown. If anything, politicians are heading in the opposite direction.

US policymakers are trying to institute a change in the law that could prove lucrative for orphan drugmakers. The so-called 21st Century Cures bill is seeking to give a six-month extension of marketing exclusivity to existing drugs that are repurposed for rare diseases.

The Congressional Budget Office reckons the legislation would cost the federal government at least $869m by 2025, and possibly more if it delays the introduction of generic "copycat" drugs seeking to treat the illnesses for which the drug was originally intended.

Others in the pharma industry warn of unintended consequences. They say that by offering drugmakers such lucrative incentives for orphan indications, they could discourage them from developing treatments for more common diseases, and thus stop them saving more lives.

Incentives can help speed drug delivery

Policy initiatives

Priority review vouchers and other 'sweeteners' have been attacked by some as giveaways, says *Andrew Ward*

When praise is apportioned for breakthroughs against rare diseases, the heroes are usually scientists, patient activists and medics. Yet there is another group, often maligned as a hindrance to innovation, that increasingly deserves some of the credit: regulators.

The surging number of treatments for rare diseases owes much to efforts by bodies such as the US Food and Drug Administration and the European Medicines Agency, to incentivise investment and to speed the journey to market when drugs are found.

Both the FDA and the EMA have orphan designations for therapies that target diseases which are either rare or for which there is no effective treatment. Drugs meeting these criteria are eligible for benefits including research grants, tax credits and up to 10 years of market exclusivity, during which regulators agree not to approve rival products. Similar measures exist in Japan.

Adam Dion, analyst at research company GlobalData, says faster access to market and relatively low development costs have caused an "infatuation with orphan drugs" across the industry.

Many orphan medicines are eligible for fast-track regulatory review because of unmet medical need. When there are existing treatments for a disease, drug companies have to clear a high bar to show that the benefits of a new product outweigh any side effects.

The bar is lower when there is no existing treatment because any benefit is an improvement and patients are likely to tolerate higher risk.

"Where there is no existing therapy, you can get to patients very quickly," says Phil Vickers, head of research and development for Shire, the Dublin-based rare disease specialist. "We are not saying we want to cut corners, but the risk ratio is different."

For drugs treating rare paediatric diseases, there are further sweeteners after approval. The FDA rewards companies with a "priority review voucher" that entitles the holder to an accelerated review of a subsequent product — not necessarily for a rare disease. In other words, even before a company reaps the benefits of its new drug, it has a head start on its next one.

Companies can monetise vouchers by selling them on in a buoyant secondary market; in August AbbVie, a US pharma group, paid $350m for the rights to a priority review granted to United Therapeutics, a smaller US company.

Further bonuses could be on the way if legislation called 21st Century Cures, passed by the House of Representatives in July, is embraced by the Senate and becomes law. The bill, aimed at promoting medical innovation, includes the promise of six months' extra market exclusivity for existing drugs that are repurposed to treat rare conditions.

To critics, all this smacks of giveaways by politicians to their deep-pocketed friends in pharmaceuticals.

"Many of the short-cuts being put forward are solutions to problems that don't exist," says Jerry Avorn, professor at Harvard Medical School, who says the pharma lobby is undercutting the FDA's role as guardian of patient safety.

> 'We are not saying we want to cut corners, but the risk ratio is different'

Industry executives insist safety is not being compromised, and say that the difficulties involved in rare disease drug development merit special treatment.

"We are often dealing with conditions that have not been investigated in a systematic way," says Geoff McDonough, chief executive of Sobi, the Swedish rare disease specialist.

Hard as the process may be, the growing number of companies chasing rare disease drugs suggests that the potential rewards outweigh the risks — just as the policymakers intended.

Patients need faster, cheaper treatment

COLUMN

Yann Le Cam

There are few better examples of European co-operation than the EU regulation on "orphan drugs", adopted 15 years ago.

Tangible benefits have been delivered to patients and international investment has come to uncharted scientific and medical areas. This has triggered innovation in life sciences and the creation of high-skill jobs, while addressing public health needs.

But more European collaboration is needed to build on this momentum and to improve access to therapies for patients. The EU has about 150 rare disease therapies with marketing authorisation, and some 1,500 in development for diseases without effective treatment.

The International Rare Diseases Research Consortium, launched in 2011, set the objective of delivering 200 rare disease therapies by 2020. This will be met by 2016.

Nevertheless, scientific advances are not being translated into therapies quickly enough. A third of patients have no access to the necessary orphan medicine; another third have access only after waiting years, as medicines are introduced first in main markets and later in others. More recently, some important medicines are not being made available because of cost.

The increasing number of rare disease therapies adds to pressures on national budgets. We need to find ways of reconciling wider access to orphan medicines with the need to make health systems sustainable.

These challenges are similar for all therapies intended for relatively small populations: paediatric medicines; gene and cell therapies; and genetically targeted precision medicines.

All stakeholders — from regulators and health authorities to the pharmaceutical industry, patients and medics — must think radically about how to get these treatments to patients faster and more affordably.

If a medicine is approved but does not reach those who need it, it fails in its objective. New R&D and business models are needed to close the gap between innovation and access. Our common objective should be more, better, faster and cheaper treatments.

Currently, marketing authorisation and reimbursement for new drugs comes at the end of clinical trials; this can take eight years, and kills many developments. For those that make it to market, there is little collection of further data showing the impact on patients. A new R&D model must include more flexible clinical trials and more innovative statistical methods.

That is to say, the production of reliable data on new medicines should no longer be primarily for the purpose of marketing authorisation, gathered mostly if not exclusively before approval. Data should be treated as a continuum and gathered throughout a medicine's life cycle: before and after approval; during R&D and patients' real-life use of the medicine.

'If a medicine is approved but does not reach those who need it, it fails in its objective' Yann Le Cam

A rare and complex disease varies a lot from one patient to another. A more systematic and deeper collection of data among the wider population of that disease enables us to identify the many variations in a medicine's effect on patients. This reduces uncertainty and helps us give the right dose at the right time for the right patient.

For severe or life-threatening diseases with no satisfactory existing treatment, conditional approvals of promising medicines should be given to save people's lives. Earlier approvals enable earlier capture of evidence.

Greater uncertainty over safety and efficacy require the participation of patients in assessing the benefits and risks of new medicines. Only patients — as experts about their own diseases — can legitimately determine how much risk or harm they are willing to accept.

This adaptive R&D model makes it possible to recruit fewer patients for trials, shortens development from five to 12 years to five to seven years and reduces the riskiness and scale of investment.

Earlier approval requires dialogue and collaboration between regulators, pharmaceutical companies, health technology assessment bodies, payers, experts and patients.

EU states' decision-making should be based first on therapeutic value, and second on value for money. For rare diseases, this is only possible through collaboration that would engage all those involved along the life cycle of medicines. Patients are calling for a smarter Europe; we urgently need a seamless approach that can bridge the gap between EU regulation and local pricing and reimbursement.

Today, European approval of an orphan medicine is made at EU level, but decisions on whether medicines should be paid for are made nationally. These assessments, disconnected from each other, do not produce a rational outcome. A huge lack of time, money and consistency can be overcome with a more collaborative approach.

Decisions on reimbursement of a medicine should remain with national authorities — but there should be pan-European co-operation.

Earlier dialogue would reduce risks and optimise benefits. And such an approach would get urgently needed drugs to patients faster — in a more attractive investor environment.

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Limited cash confronts regulators with difficult choices

Ethics

With families desperate for the green light on drugs, tough decisions can cause pain, writes *Andrew Ward*

When the first treatment for a rare genetic disorder called Morquio syndrome was approved by EU regulators last year, medics hailed it as a triumph for UK research as well as for the 88 people — mostly children — living with the disease in England.

Many of them had taken part in trials of the medicine, called Vimizim, at the Royal Manchester Children's Hospital — the only centre in the world to have been involved in every stage of clinical research into the product.

It was, said Professor Sally Davies, UK Chief Medical Officer, "an excellent example" of how the NHS provided "the best possible environment for health research".

Yet, almost 17 months after marketing authorisation was granted, Vimizim is still not funded by the health service that helped prove its efficacy.

The case of Vimizim, also known as elosulfase alfa, is a stark demonstration of the complex ethical and economic dilemmas surrounding adoption of expensive rare disease drugs.

These tensions are especially acute in the UK as the country battles to contain the rising cost of its cherished but creaking public health service in an era of fiscal austerity and an ageing population.

Morquio involves the build-up of large sugar molecules that the body cannot break down, causing damage to tissue and organs.

This leads to a range of symptoms affecting the heart, lungs, spine, breathing, sight, hearing, mobility and growth. Average life expectancy of people with the disease is about 30.

Until recently there was no treatment, but that changed last year when Vimizim, made by US-based BioMarin, was approved by regulators on both sides of the Atlantic. Results from clinical trials found that, after 24 weeks of treatment, patients could walk an average 22.5 metres further in six minutes than those taking a placebo. Dr Simon Jones, the paediatrician who led the Manchester study, described the drug as "an exciting development" that offered "the potential to slow the progression of this devastating disorder".

For NHS authorities, however, the benefits must be weighed against its price.

Like many rare disease therapies, Vimizim is very expensive at £395,000 per person per year, because its development costs must be recouped from a relatively small number of patients.

> Tensions are acute in the UK, given the rising costs in its cherished but creaking public health service

BioMarin supplies the drug free to those who took part in its trials while it awaits a decision, but long-term availability will rely on a green light from the National Institute for Health and Care Excellence (Nice), the agency that assesses value for money in the NHS.

In a provisional ruling in June, Nice said it was "minded not to recommend" Vimizim because it felt BioMarin had "overestimated the clinical benefits" in the economic model used to justify its price. However, this month, after further discussions — including the offer of a confidential discount from the company — Nice changed its mind and issued a provisional recommendation for its adoption by the NHS. A further consultation is under way before a final decision in January.

The case is being closely watched because Vimizim is among the first drugs evaluated by Nice under a new process for assessing "highly specialised technologies" which are too costly to win approval through the agency's usual value-for-money criteria.

For people suffering Morquio and their families, the protracted argument over health economics has been deeply frustrating. While they wait for Nice to decide, Vimizim is already being funded in more than 20 European countries.

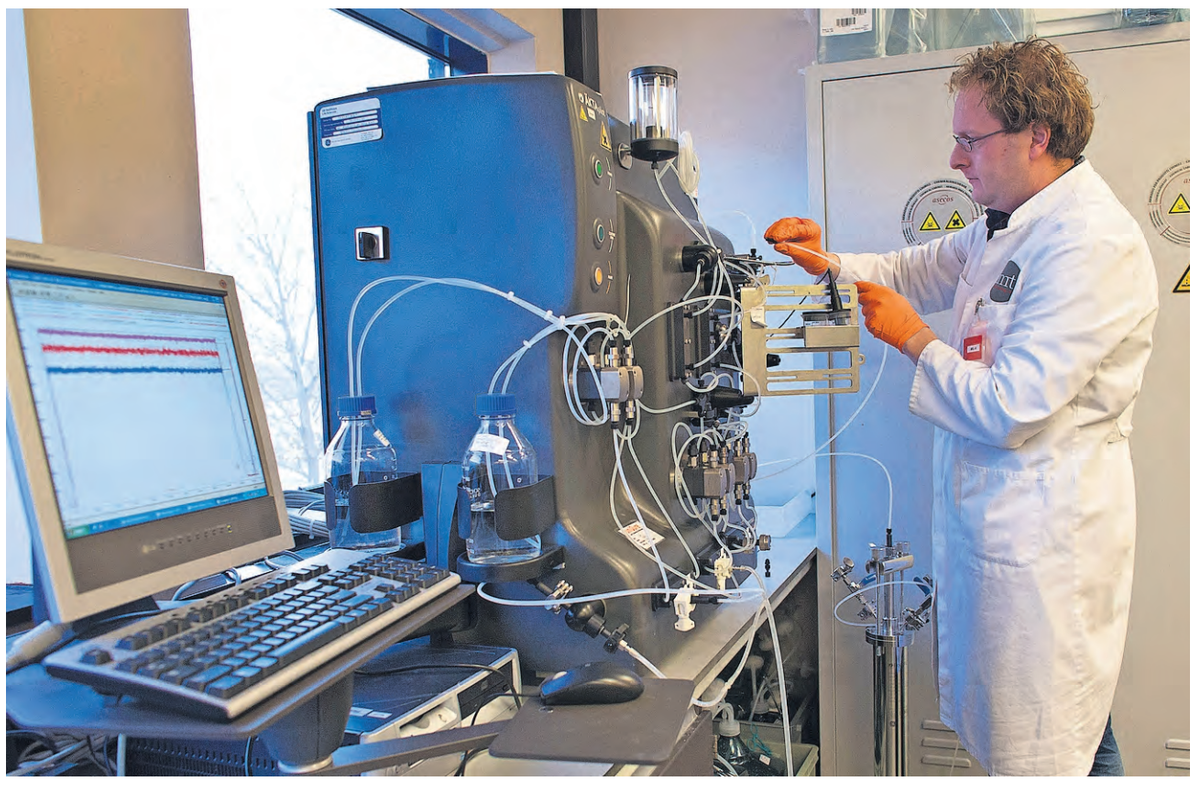
Christine Lavery, chief executive of the Society for Mucopolysaccharide Diseases, whose son died from a related condition, said families had been "emotionally drained" by the delays. Among them are Vikki and Dean Brown from south London. They describe their six-year-old son Harvey as "a bubbly, fun-loving little boy" but he is unable to run around or play football with his friends, and frequently wakes at night crying with pain from Morquio. "We are losing faith in our country and health system, knowing that if our son was born in France, Germany or many other countries, the treatment would be funded."

In a parliamentary debate on the Vimizim case this year, George Freeman, UK life science minister, warned that tough decisions were unavoidable as medical advances brought more specialist treatments for genetic disorders. Services for rare conditions already account for 14 per cent of annual NHS spending at £14bn, he said.

"The painful truth is that, with finite resources, when we make a decision in one case to accept a drug, we will make a decision elsewhere to reject, and we have a duty to all to ensure that we make those decisions fairly."

A technique whose time may at last have come

Gene therapy Renewed optimism has begun to sweep over the field, reports *Clive Cookson*



Potential: at work on Glybera at UniQure
Michael Kooren / Reuters

The era of clinical gene therapy began 25 years ago this month. A four-year-old American, whose immune defences were destroyed by a rare genetic defect, received a transfusion of her own blood cells to which healthy copies of the faulty gene had been added. She went on to attend school and now leads a normal life.

Dozens more clinical trials soon got under way, amid great hope and hype, and analysts forecast sales of genetic drugs worth more than $1bn by 2000, and tens of billions of dollars by 2010.

Fast forward to now. The market value is negligible and the US Food and Drug Administration has not approved a single gene therapy product.

Only three are available anywhere in the world: two in Asia for rare cancers and one, Glybera, approved by the European Medicines Agency for an ultra-rare blood disease. UniQure, a Dutch biotech company, is expected to start selling Glybera this year as the world's most expensive medicine, at a price above $1m per patient.

Compared with expectations in 1990, gene therapy has so far been a dismal disappointment. It turned out, for example, to be far harder than expected to find good vectors to carry replacement genes safely and efficiently to the tissues where they are needed. Development was set back for several years after the death in 1999 of Jesse Gelsinger, a teenage patient in a gene therapy trial.

But now a feeling of optimism is apparent in the field, as more appropriate vectors are developed and a wave of clinical trials delivers promising results.

At the same time, more funds are being made available for gene therapy by pharmaceutical companies, large and small, as well as by public bodies and medical charities.

There have been several encouraging developments this year. Bristol-Myers Squibb, the US pharma giant, concluded a complex collaborative deal with UniQure, which will see BMS putting several hundred million dollars into the Dutch company. UniQure has an impressive portfolio of gene therapy products in development besides Glybera. These include treatments for forms of haemophilia, porphyria, Parkinson's disease and heart failure.

The UK's GSK submitted an application to the European Medicines Agency for what is likely to be the second gene therapy product to go on sale in the west. GSK2696273, developed with Ospedale San Raffaele in Italy targets a failure of the immune defences called ADA-SCID, which affects 14 children a year in Europe.

Patrick Vallance, GSK head of pharmaceutical R&D, says: "We believe this marks a significant milestone, showing the potential of gene therapy as an important . . . modality for tackling the underlying cause of serious diseases."

GSK has gene therapies in trial for two other rare diseases in collaboration with San Raffaele: metachromatic leukodystrophy (a toxic build-up of lipids in the white matter of the central nervous system) and Wiskott-Aldrich syndrome (a complex condition affecting the blood and immune system).

Other companies actively involved in gene therapy R&D include Oxford BioMedica, Bluebird Bio, Taxus Cardium, Juventas Therapeutics, Mesoblast and Sangamo BioSciences.

Sanjeev Kumar, analyst at consultancy Frost & Sullivan, says about two-thirds of the trials in progress target cancer. Single-gene defects such as haemophilia, thalassaemia and cystic fibrosis are the next largest category. Others are treating cardiovascular disease, and central nervous system and eye disorders.

A good example of the long-term nature of this research is the effort to find a treatment for cystic fibrosis (CF). As soon as scientists discovered in 1989 that mutations in a gene called CFTR were responsible for CF, they began planning ways to introduce healthy CFTR into patients' lungs.

> Analysts are excited again as talk resurfaces about $10bn sales in 10 years

As with other gene therapy projects, it turned out to be harder than expected. The UK Cystic Fibrosis Gene Therapy Consortium was formed in 2001; after much experimentation, it designed a clinical trial with £3m funding from the Medical Research Council and National Institute for Health Research.

The first positive results — showing modest but significant benefits to lung function — were reported this July in a trial with 136 CF patients. They inhaled normal copies of the CFTR gene wrapped inside microscopic fat globules.

The consortium expects to make the treatment more effective in two ways.

One is to add more DNA to the liposome and combine it with "potentiator" drugs to increase the gene's activity. The other is to use a harmless virus instead of the liposome to carry the gene into the lungs; viruses are the most widely used vectors for gene therapy.

Analysts are excited again as talk resurfaces about $10bn sales in 10 years.

Given the field's record, such forecasts may seem overambitious but the example of monoclonal antibodies — another technology that disappointed for many years and then zoomed into the pharmaceutical stratosphere — illustrates the slow-burning potential of some biomedical advances.

Charities urge low-income nations to recognise need

Aid

Companies and individuals work to educate parents and governments and alleviate suffering, writes *Andrew Jack*

Hawa Dramé understands rare diseases in the developing world like few others. A geneticist by training who lost two of her children to orphan ailments, she worked for patients groups in Europe before returning to Africa to create foundations called Fitima in her native Guinea and in Burkina Faso.

"In Europe, the problem of rare diseases is difficult. But in our countries it is a desert," she says. "There is no social security, few specialist doctors and few who are interested. We have a problem of human resources: there is no training in west Africa for paramedical skills."

With the costs of orphan treatments so high, and no medicines at all for many conditions, her organisation has focused instead on supporting patients and families. "The minimum we can do is to stop or attenuate these conditions."

She says that where families once simply gave up on children with such conditions as the result of fate, she works to educate people on local radio and television and to make society appreciate that patients' lives can be improved. She has also created a special school, and offers support and counselling: "We are showing that a handicap is not a fatality."

Carlo Incerti, senior vice-president of Genzyme, one of the leading producers of orphan drugs, is also cautious about fixating on costs and supplies as a barrier.

"Donating drugs is not enough," he says. "You need diagnosis, knowledge and follow-up. You have to be in the country, not just parachuting in drugs."

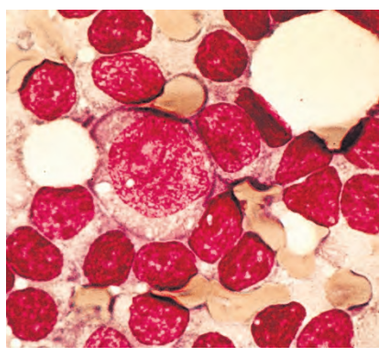
He estimates that his company has provided humanitarian treatment to more than 1,700 patients in some 55 countries — often alongside the charity Project Hope providing logistical support. That includes work in Afghanistan, Pakistan and Palestine, where staff from the company's Israel office volunteer to provide treatments free to children — even during periods of conflict. "I have never seen a patient left untreated because there is no immediate possibility of reimbursement," Dr Incerti says. Nonetheless, his company seeks in the medium term to find ways to make authorities contribute financially. "Treating one or two patients in a country is not profitable, but it makes governments recognise the disease and start to make contributions."

However, he points out that there are many practical barriers to delivering medicines in low-income countries — not least obtaining import licences, which can hold up life-saving treatments for months.

Similar frustrations have been faced by Tim Eden, medical adviser to World Child Cancer, which supports treatment of acute lymphoblastic leukaemia (ALL), among other conditions, in low-income countries.

He has been frustrated that while newer forms of asparaginase, the pivotal treatment, are very expensive, lower-cost generic alternatives have seen concerns raised over quality.

Mr Eden has struggled to identify the source of drugs acquired by local clinics.



Treatment: ALL is among conditions that hit some developing countries

"It is a nightmare," he says, as he calls for consistent global standards with scrutiny by the World Health Organisation to ensure minimum requirements.

For John Forman, former director of the New Zealand Organisation for Rare Disorders, the incidence of people failing to get treatment because of their inability to pay remains enormous.

"In developed health systems, usually about 95 per cent of patients needing orphan drugs will receive treatment, whereas in the developing world, probably 95 per cent or more aren't treated," he says.

Yet such issues of cost and access are not exclusive to developing countries.

Yann Le Cam, head of Eurordis, the European patients' group for rare diseases, says: "It's more and more difficult to speak about high- and low-income countries, but rather about high- and low-income people. There are plenty without access in the US and the EU."

He calls for mutual recognition by authorities, with a shift to international regulation and price negotiation (*see page 3*). "We need to create a global market and still make orphan drugs affordable and sustainable."

In the meantime, Mr Le Cam expresses some satisfaction with government progress in regions including eastern Europe and Latin America. They have established regulations and reimbursement for orphan treatments, amid fresh efforts by patient groups to combine forces.

"There are 200m people with rare diseases around the world," he says. "We are going to need more international co-operation."

Sharing data and exome sequencing offer progress

Diagnostics

Analysing the genes that code proteins is cheaper and faster than conventional tests — and can yield better results, says *Sarah Murray*

Before the advent of genomic sequencing, those with rare diseases often felt, as one family put it, they were "wandering aimlessly in a new city in a fog".

After sequencing, the family — quoted in a report by the Rare Genomics Institute — felt they had "a map and lights". But while genomics offer new possibilities, data sharing and social media also play a critical role in spreading the knowledge.

Because about 80 per cent of rare diseases have identifiable genetic origins, the sequencing of the human genome created opportunities for diagnosis.

"Diseases that are genetic are being discovered at a pace that's astonishing," says Jimmy Lin, head of the Maryland-based Rare Genomics Institute. Add in rapidly dropping sequencing prices and what took two years to do five years ago, now takes a few days.

While full sequencing is not always affordable, exome sequencing, which searches protein-coding genes for mutations, is being taken up more frequently. Compared with dozens of tests of single genes, exome sequencing is far cheaper — and often delivers better results.

"It's definitely cheaper," says Andrea Epstein of the patient advocacy group Global Genes. "It's at least half what an insurer would be paying [for diagnostics that do not use sequencing]," she says.

"And it would in many cases get information that could lead to better opportunities for treatment."

Of course, while prices are coming down, exome sequencing is unaffordable for some, and insurance companies do not always cover the cost. This means that educating insurers on the value of genetic testing will be an important step in increasing its adoption.

Nevertheless, despite the advantages, the testing does not necessarily lead to concrete answers. Depending on the position of the mutation along a gene, some people will get the disease while others will not, says Dr Lin.

"If you match an existing gene that is known to cause a specific disease, you can't be 100 per cent sure that the mutation of that gene in that position necessarily causes the disease," he explains.

And when it comes to discovering new diseases, the uncertainty is greater. If a mutation is found in both parents and child, it may be the likely culprit. "But because these diseases are rare, without finding other families or doing further studies, these are guesses," says Dr Lin.

For this reason, the sharing of genomic and clinical data is seen as an increasingly important part of diagnosing rare diseases. "There's lots of momentum behind data-sharing between clinical institutions, physicians and patients," says Ms Epstein. "If two people in the world have the same rare variant, those two doctors can share information on the symptoms."

One organisation that promotes data-sharing is the Global Alliance for Genomics and Health. With 300 partners, its goal is the "responsible, voluntary and secure" sharing of data.

Meanwhile, GenomeConnect has created a registry where patients can share information securely. Other collaborative efforts include the International Rare Diseases Research Consortium, which brings organisations together.

> 'Diseases that are genetic are being discovered at a pace that's astonishing'

Technology will be a critical tool in all this. "It will become increasingly useful to enable people to find similar patients," says Maureen McArthur Hart of Global Genes.

She cites the case of children with NGLY1, which causes developmental delays. "Through social media, their physicians and families realised they had the same syndrome as others and subsequently found other children around the world who have it."

However, since many of these initiatives are designed for clinical data, US non-profit Syndromes Without A Name (Swan) is developing a resource where people can describe the signs and symptoms of a family member.

Those that have undergone exome sequencing can add that to the pool of information.

"Families have a lot of knowledge, but sometimes they don't know what to do with it," says Amy Clugston, president of Swan. "We use families as a resource and a partner in this."