Orphan Drug Market Access: Opportunities & Challenges

About 30 million people in the European Union are living with a rare disease, and there is an estimated 25 to 30 million people in the US who have been diagnosed with a rare disease. However, the definitions of what constitutes “rare” are different globally. There may be as many as 7,000 individual rare diseases. In the US, this includes conditions affecting fewer than 200,000 in the country. In the EU, a rare disease affects fewer than 1 in 2,000 people. The number of patients suffering from one of these diseases is often very small, but rare diseases affect a significant portion of the global population. Orphan designated diseases are an increasing part of the pharmaceutical industry, providing 18% of revenue, and estimated to rise to 22% by 2022.

Therapeutic candidates with Orphan Drug Designation in the US benefit from development incentives, including tax credits for qualified clinical testing. Also, a marketing application for a prescription drug product that has received orphan designation is not subject to a prescription drug user fee in most cases. Orphan products are often expensive for payers and patients. Looking at 2017 data, reports have placed the median annual cost for an orphan drug in the US at approximately $46,800. Though costs for drugs treating the top 10 rare diseases are lower.

This e-book includes features on market access strategies in the US, Europe and further afield, with a specific focus on prescription drugs for rare diseases. For example, one article explores the use of orphan drugs in emerging markets and the different strategies required. Emerging markets and orphan drugs are two of the most rapidly growing sectors for the pharmaceutical industry. Just one issue highlighted here, though, is that developing countries often have limited health care budgets and may not have accurate data on the local prevalence of a disease. These regions require a different access approach compared with markets that have established and sophisticated health care systems.

Lucie Ellis
Managing Editor, In Vivo
Informa Pharma Intelligence

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Gene Profiling Identifies Drugs For Childhood Cancers But Access A Problem

BY ANDREW MCCONAGHIE

A new study has shown that genetic testing can help match children with cancer to targeted drug treatments, opening up hope of improved outcomes for young patients with hard-to-treat conditions.

The test developed by The Institute of Cancer Research (ICR) in London is a first for pediatric cancer treatment and could prove to be a foundation stone in making precision medicine a reality in the UK.

But in highlighting the potential of genetic testing, the study also made clear how England’s National Health Service (NHS) currently lacks an infrastructure for identifying these mutations and ensuring these patients have the chance to access targeted medicines.

Led by ICR and The Royal Marsden NHS Foundation Trust, researchers used a gene panel test to read the DNA sequence of 91 genes that drive cancer’s growth and spread from 223 children’s tumor biopsies, looking for mutations treatable with targeted drug therapy.

At least one genetic mutation was detected in 70% of samples processed by the next generation sequencing (NGS) panel, and overall 51% were clinically actionable. However the study found only 7% of those with targetable mutations were able to access the appropriate drug licensed for use in adults.

Researchers found a number of reasons for this, including a lack of available clinical trials, difficulties accessing novel drugs on a compassionate-use basis and/or clinical deterioration of the patient.

The children involved in the study had a range of solid tumors, including neuroblastoma, rhabdomyosarcoma, glioma and other non-CNS solid tumors.

Although many patients had relapsed/refractory disease, many were still on either first-line therapy or proven standard relapse therapies at the time of sequencing. A number of patients were also enrolled in available Phase II trials that did not require biomarker screening.

The most common potentially treatable mutations were in the genes ATRX, CDKN2A and CTNNB1, each found in 12 children’s tumors. MYCN mutations were found in 11 tumors and PI3K3CA mutations in 10 tumors.

Three children had BRAF gene mutations, common in melanoma skin cancers and treated using Novartis AG’s targeted combination therapy of Tafinlar (dabrafenib) and Mekinist (trametinib). (Also see “Novartis’ Growth Driver Tafinlar/Mekinist Picks Up New Melanoma, Thyroid Indications” - Scrip, 7 May, 2018.) Using this combination, one of the children had their brain tumor held in check for 13 months before developing resistance. Another was on the drug for nine months with no progression of disease. The third child could not tolerate the combination but had a response to dabrafenib for 15 months.

This illustrates the potential benefit to a wider population of children with cancer and study author Sally George, a consultant pediatric oncologist at The Royal Marsden, said, “Children deserve the very best cancer treatments, so they can live as long as possible and as well as possible. We desperately need better, more intelligently designed treatments which can give children longer with their families with fewer side effects.

“By testing tumors for specific gene mutations, we have shown it’s possible to identify new smarter, kinder treatment options for children, which may potentially give these patients much longer with their families after conventional therapies have failed.

“But our study also exposes the desperately frustrating barriers that children still face in receiving new treatments - barriers which lie in the regulations controlling how drugs for children are developed and approved.”

Plans to address the need for routine genetic testing and access to targeted medicines is addressed in the NHS Long Term Plan, which was published in January 2019.

It includes a pledge to make the NHS the first health service in the world to offer whole genome sequencing for children with cancer and young people who have a rare genetic disorder, in addition to adults suffering from certain rare conditions or specific cancers.
New Science As A Business Growth Strategy
THREE DIMENSIONS TO GUIDE THE TRANSITION FROM OLD TO NEW

BY SANJKRITI THAKUR & GORDON MURPHY

Finding innovative ways to adapt the biopharma business model to external and internal challenges is a key competitive differentiator for today’s C-suite leadership.

Finding innovative ways to adapt the biopharma business model to external and internal challenges is a key competitive differentiator for today’s C-suite leadership. The stark choice is to disrupt – or be disrupted. Accenture’s work with numerous life sciences companies over the past few years reveals there are two typical types of disruption, each requiring a different strategic and organizational response. The first is that intuitively self-evident “big bang” disruption where a new innovation revolutionizes an entire industry and causes major and immediate change. The second is “compressive disruption” where a series of smaller innovations slowly build over time, and depending on other external factors, are often unnoticed and lead ultimately to a crisis of decreasing profits in the disrupted companies.

Our conclusion is that compressive disruption is the bigger threat to the health of the biopharma business model because it allows for complacency when what is really needed is proactive initiative and a change in mind-set, both of which are difficult to implement in large organizations that tend to be resistant to change. In contrast, the response to compressive disruption demands a turnaround in basic strategy that is relentless in generating value from every investment it makes, from the discovery phase right through to patent expiry, and involving a range of inputs that include applied tools and technology as well as the products of scientific discovery and research.

Accenture recently published a white paper, New Science: Biopharma’s New Growth Machine, to showcase the merits of how New Science can itself be the antidote to compressive disruption by keeping companies fixedated on being first to “get to what’s next” in unmet medical need – staying on the vibrant edge of science, rather than safely in that middle ground of institutional status quo. Often too much focus is given to the hottest cutting-edge science, while incremental areas of growth are overlooked.

This article drills down into how to approach the innovative impulse structurally, by identifying several “archetypes” that life sciences companies should emulate in institutionalizing New Science to generate a predictable – and progressive – gain in revenues from their biopharma investments. By applying this construct to their own operations, management can anticipate, track and assess the strategic imperatives shaped by these archetypes – and bridge that transition gap from old science to the new.

Exhibit 1. The Three Dimensions Of New Science

<table>
<thead>
<tr>
<th>NEW TREATMENT SCIENCE</th>
<th>NEW PATIENT SCIENCE</th>
<th>NEW TECH SCIENCE</th>
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<tr>
<td>Scientific product advances, including new mechanisms of action, therapeutic classes, drug discovery pathways and formulations that add value to patient outcomes, as well as the more usual scientific progression into new targets.</td>
<td>Advance aimed at addressing patient or population unmet needs and driving value areas historically underserved by the pharmaceutical industry. This includes new indications, patient subgroups, or eras of unmet need, small patient pools and new therapies that dramatically increase the standard of care.</td>
<td>Products with regulated technological innovations augmenting scientific and patient value independently or with a traditional medicine. This includes new health technologies, devices, diagnostics, biomarkers, apps, analytic tools, genomics and companion devices.</td>
</tr>
<tr>
<td>The dimension that triggers questions about where we should be investing for therapeutic novelty and for return on investment.</td>
<td>The layer that reveals those who lead or fail to support and invest in global health and therapeutic areas where need is unmet.</td>
<td>The element of technology convergence designed to expand definition and process of therapeutic innovation and approval.</td>
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As the science in the pharmaceutical industry is broken down into its constituent parts, products

September 2019
can be categorized by the type of science, and the type of “New.” Exhibit 2 provides an overview of the historic and projected revenues for launched products in the prescription pharmaceutical industry categorized by the dimension of science affecting the treatment or patients. Tech Science has not been included in this analysis as its application is more complex and the field is comparatively new, but its general characteristics are summarized below.

**Bridging Old And New Science: Selecting Dimensions And Archetypes**

What about the conventional way of approaching science, or what we refer to as Old Science in New Science: Biopharma’s New Growth Machine? Although relatively stable in value, Old Science makes a steadily decreasing contribution to the total growth of the industry, while the future growth of industry revenues is largely driven by the introduction of New Science. Therefore, trade-offs must be made to navigate the span between Old and New Science.

Within New Science there is a stable proportion of revenue from New Patient Science by itself (i.e., around 6%), but the proportion of revenue from New Patient Science increases when combined with New Treatment Science (25% or $170bn, in 2018; rising to 29%, or a projected $252bn, in 2022). This suggests that although using Old Science methods in new indications still retains some value, most of the growth in New Patient Science is from the combination with New Treatment Science. Therefore, we conclude there is only limited value in tackling a new patient group using standard methods, but that using new methods to tackle new patient groups could be a substantial engine for growth.

New Treatment Science by itself is slowly increasing as a proportion of pharmaceutical revenue, as well as increasing in value ($88bn in 2012 to $127bn in 2018) but the fastest growth in New Treatment Science is seen when it is combined with New Patient Science. All forms of New Treatment Science made up 43% of revenue in 2018 and are projected to reach 48% of revenue in 2022, making this a very valuable dimension of science in total.

Although all of the sections analysed here increase in value over time, the fastest growing archetype for projected market share and projected value is the combined New Patient Science and New Treatment Science. The size of the effect of New Science on current and projected prescription pharmaceutical revenues suggests that valuable insight can be gained by breaking each dimension down into its constituent archetypes.

Each dimension of New Science can be described using different archetypes and can be analysed in various ways, and at different points in the value chain. Archetypes may include drug combinations. This section describes the different archetypes of New Science, and their application.

**New Treatment Science: Benefits From New Methods Of Managing Diseases**

New therapeutic targets are a common aspect of New Treatment Science, and much of the traditional methodologies of driving growth in the pharma industry can be attributed to R&D in this area. New mechanisms of action are a closely related and a frequent source of New Science, but require a more innovative approach than new targets, for example the use of exon skipping through novel platform RNA splicing to treat Duchenne muscular dystrophy.

At a higher level, but much less frequently, new therapeutic classes can drive New Science, with RNAi drugs as a prominent example. Another frequent source of New Science is innovation around new drugs as a prominent example. Another frequent new science is innovation around new therapies, for example the use of exon skipping through novel platform RNA splicing to treat Duchenne muscular dystrophy.

**New Patient Science: Innovations To Develop And Commercialize Treatments In Underserved Populations**

The traditional angle of addressing new patient populations is to move into new indications. Although this remains a substantial revenue-generating archetype, revenues for this archetype are slowly becoming a smaller proportion of the total prescription pharma market.
illuminates this, with first-to-indication drug revenues, a historically important growth area, being roughly stable from $77bn in 2012 to $76.6bn in 2018 and a projected $74.3bn in 2022, but with a decreasing percentage of the total pharma market: from 13% in 2012 to 11% in 2018 and a projected 8% in 2022. In the context of the number of untreated indications decreasing over time, and a commercial focus on treating the more profitable indications leading to less profitable indications remaining, this suggests two things:

- First, focusing on new indications and untreated populations still maintains value for those who choose to continue R&D in these areas.
- Second, it will be increasingly difficult to grow market share; stagnation is likely if investors don’t pivot into a new scalable growth strategy.

Although the core focus of trying to treat the untreated indications will maintain revenues for a while, failure to think long term and make investments into research and development or strategic acquisitions to drive new areas of New Science now could lead to eventual decline, irrelevance and business failure.

One area of New Patient Science is focusing on areas of unmet need, or where drugs can have a large impact on the standard of care. The needs of patients for expedited approvals for serious conditions, or drugs that potentially have a large impact on the standard of care has been recognized by the FDA, which since 2012 can assign breakthrough therapy designation to development programs. Since inception of the classification, approved breakthrough therapies have rapidly gained share in volume and value, and by 2022 breakthrough designated therapies are forecast to make up 15% of total prescription pharma revenues. It can be expected that the effect of a new regulatory process increases from inception, but what is quite telling is the continuous increase in value and proportion of sales, neither of which show signs of slowing. This indicates that breakthrough designated therapies could become a major source of revenue for the pharmaceutical industry even more so than they are now, and therefore that investment into areas with high unmet need will continue to be lucrative.

Similarly, areas with low number of patients, such as rare diseases, are another growth area for New Science. Orphan designated diseases are an increasing part of the pharmaceutical industry, currently providing 18% of revenue, and estimated to rise to 22% by 2022. Another area of New Patient Science is looking into opportunities presented by populations with high unmet need due to levels of income, or area specific diseases. According to a May 2019 10-year analysis by the Access to Medicine Foundation, people living in low- and middle-income countries (83% of world population, but only 25% of projected 2020 pharma spend) may struggle with access to medicine. An estimated 2 billion people currently have no proper access to medicine. The same report discusses the trends in some pharma companies into R&D to tackle these issues, including neglected tropical diseases. In an increasingly competitive environment, with growing societal pressures, this new area of interest could become an important investment to protect revenues.

Of course, New Patient Science has implications largely for the patients, but also drives investment in companies attempting to tackle orphan or rare diseases, many of which are genetic, as well as anti-infectives and vaccines. Added benefits from New Patient Science include improving patient visibility in infectious and vaccines. Added benefits from New Patient Science include improving patient visibility in tropical diseases. In an increasingly competitive environment, with growing societal pressures, this new area of interest could become an important investment to protect revenues.
New Technological Science: Using Technology To Improve Outcomes Or Drive Drug Discovery

These technological innovations are an emerging dimension, driving patient value in improving treatment, care and access. As a relatively new area, the impact is more difficult to measure; however, we expect the opportunity to be very large.

The biopharmaceutical industry is slowly moving from a one-size-fits-all approach to one where treatments are personalized to each patient. This is considered an area where substantial improvements can be made in treatment outcomes, and regulatory authorities have recognized these by committing to accelerating personalized medicines. Significantly, 42% of medicines approved by the FDA in 2018 received this designation (see Exhibit 6). Personalized medicines include innovations such as using unique biomarkers or personalized molecular targets.

Digital interventions targeted at improving patient access and experience is another area of New Tech Science. The first wave of tech-based interventions in medicine were focused around home monitoring and diagnostics, but now we see an increase in tech-based innovations to improve patient access and patient adherence, often designed to work closely with the treatment regimen. In practice, this can be seen with Abilify MyCite, an oral pill that is embedded with sensors to track patient adherence, and with disease management systems such as WellDoc, which helps patients manage their diabetes and interfaces with health care professionals. Other innovations include companion diagnostics and point-of-care tests.

Wearable technologies are another rapidly growing sub-archetype of New Tech Science. Innovations such as Quell, an FDA-cleared device, have shown to be effective at helping to alleviate symptoms of patients suffering from chronic pain.

The digital interventions archetype of New Tech Science is a relatively nascent area of growth but shows rapid growth prospects with increased venture and private investments into the space. According to CBInsights, in 2018 alone, health technology received $7.9bn in venture investments.

New Tech Science extends further than just new digital and new devices. Other technological innovations are included, such as new analytics and new evidence, including the use of real-world evidence (RWE). RWE is an area of great interest and has been successfully used in improving clinical studies and pharmacovigilance. Its applications will eventually extend to improving efficacy of drug discovery and reducing timelines. The use of analytics extends into genomics and can be applied to drug development. Early movements here include the partnership between 23andMe and GlaxoSmithKline PLC.

New Tech Science has implications for both patient outcomes and pharmaceutical revenues, and for the discovery of new therapies. Already increased adherence can be seen with products like AdhereTech's smart pill bottle, which in partnership with Diplomat Pharmacy has shown a 12% increase in patient retention, an increase in the number of refills per patient, and a decrease in the number of days without treatment. Investment into analytics can be seen in the Bristol-Myers Squibb Co. and Concerto partnership to use eurekaHealth, Concerto's AI and machine learning platform. Concerto's tool uses real-world data to accelerate insights through novel health economic outcomes and clinical development studies. Concerto has also been partnering with other companies, including Pfizer Inc.

New Tech Science has many implications for the industry, which is creating more and deeper partnerships to take advantage of this new area. Products such as companion diagnostics also require joint regulatory approval. Digital medicines also allow different types of companies to develop and operate in the industry, reducing barriers to entry.

For the immediate future, these leaders are increasing investment, partnerships and acquisitions in the existing areas of New Science. Over the long term, real leadership may require a more proactive approach involving integrated New Science development platforms linked to advanced predictive analytics and intelligent solutions software.

Integrating New Science development approaches will involve moving expertise that is currently external in-house. Partnerships with external companies work well for short-term solutions, or to take advantage of low-hanging opportunities, but many such external providers do not have access to knowledge and expertise unique to the life sciences sector. Innovations coming from the external side often focus on simple concepts or reinforce a small angle of expertise of the founders, applied through existing infrastructure. To lead in the future, expertise in digital needs to be embedded in the organization to take advantage of valuable opportunities. In other words, biopharma companies need to start treating digital R&D similarly to that of their drug R&D, chiefly by accepting the risk profile required for new ideas to be tested.

Intelligent solutions provide further opportunities to lead in the future. Many products are logic-led, starting with what we know and investigating that for tracking or predictive capabilities, potentially then with intelligent solutions. This is great for taking advantage of what is already known; however, that uses a fraction of the information available in what is a data-rich environment. Future leaders should look to use what we do not know and have data lead New Science. Intelligent platforms with integrated data sources, could identify opportunities, in prediction and evidence to discover relationships between variables that may otherwise not be obvious. This would allow for more innovative design of New Science products. Pharma companies have been looking at this for a while with therapies, but data leading New Tech Science, or data leading New Patient Science, could become very valuable.

Exhibit 6. Proportion Of FDA Approvals For Personalized Medicines

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The current discussion on US pharmaceutical pricing also has a number of potential effects on the winners from New Science. Personalized medicine is unlikely to have a lower price threshold than many alternatives. In fact, New Patient Science is unlikely to be low cost where patient pools are small. Thus, the conclusion is that not only is New Science fueling the debate on pricing, it is also impacting investment decisions, with potential effects on the patient interest in keeping the progress around innovation alive.

In conclusion, our analysis of launched products has demonstrated that a large proportion of recent pharmaceutical market revenues have originated from New Science. Each dimension is a growing part of the pharmaceutical industry, with different growth characteristics. Although New Treatment Science contains many traditional directions for innovation, the greater potential of this dimension can be realized when combined with New Patient Science, which itself is an area of increasing potential. New Tech Science is an emerging area of increasing interest to the industry and has already been able to demonstrate improved patient outcomes, even in these early stages.

All told, New Science in each dimension is a driver for growth and opportunity in an increasingly complex biopharma industry. This is driving improvements in patient outcomes and the ability to address unmet need in different populations, and is driving the formation of start-up enterprises as well as acquisition of companies innovating in New Science.

The fact is the New Science dimensions and archetypes will allow the C-suite to obtain a fuller understanding of the present and future states of a company and the wider industry that surrounds it. This analysis observes companies moving across simpler product models to more advanced models. At the foundation, the determination of where they land is the combination of New Science in their portfolios.

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Full Pediatric Labeling Is Lacking For One-Third Of Orphan Drugs, US FDA Finds

BY BRIDGET SILVERMAN

The US Food and Drug Administration’s efforts to improve drug labeling for pediatric patients have been making solid gains in orphan drugs, with the number of orphan products approved with full pediatric labeling hitting a peak in 2015-2018, according to an agency report to Congress.

The FDA analyzed 20 years of orphan drug approvals for the report, which was required by the 2017 FDA Reauthorization Act, or PDUFA VI, to evaluate “the lack of information in the labeling of drugs for indications that have received an orphan designation ... with respect to pediatrics.”

A working group including the Office of Pediatric Therapeutics, the Division of Pediatric and Maternal Health, the Center for Drug Evaluation and Research (CDER) and the Center for Biologics Evaluation and Research (CBER) identified 548 orphan indications approved between April 1, 1999 and August 31, 2018. Only 348 indications (64%) were found to be “relevant to children, thus warranting pediatric use information in the labeling for the indication.”

“FDA has seen an increase over time in the number of approved orphan products with indications (some products were approved for multiple indications) that are fully labeled for pediatric use,” the report states. “This increase is most notable over the last 3 years.”

Of the 348 pediatric-relevant approvals, FDA categorized 221 (64%) as “fully labeled for pediatric use,” meaning the label contained “adequate efficacy, safety, dosing, and age-appropriate formulation information to support its use in the full range of affected pediatric patients.”

The data to support full labeling can come from sources beyond “pediatric trials conducted by the sponsor for the orphan indication,” according to the report, including “published literature, extrapolation of efficacy from adults or other
Companies Urged To Tailor Approach To Orphan Drugs In Emerging Markets

BY JOHN DAVIS

C onventional marketing strategies for orphan drugs, that target key decision-makers and clinical stakeholders, may not be effective in emerging markets where payers usually prioritize the medical needs of larger patient groups, and companies should adapt their business models to be successful in such countries, says a new report.

Emerging markets and orphan drugs are two of the most rapidly growing sectors for the pharmaceutical industry, but developing countries often have limited health care budgets, and may not have accurate data on the local prevalence of a rare disease, says the report’s author, marketing consultant Ben Shankland, in a new Datamonitor Healthcare report, Orphan Drug Access and Pricing in Emerging Markets.

Clinicians in emerging markets may be over-burdened by having to treat more prevalent conditions than orphan diseases, and primary care networks to identify sufferers may be lacking. “Industry therefore faces the dual challenge of identifying not only patients, but also the clinicians who have sufficient expertise and influence to deliver funded access to orphan drugs,” the report says. And on the payer side, rigid market access systems may not be flexible enough to accept the clinical and economic evidence associated with new orphan drugs.

Labeling Lacking For Youngest Patients

Inadequate pediatric labeling was noted for 127 of the 348 orphan indication approvals relevant to children. The group contains some repeat offenders: the 127 orphan indications missing pediatric information in labeling corresponded to 98 drugs, thanks to multiple orphan indication approvals for 19 of the 98.

No pediatric information at all was identified in labeling for 81 of those 127 approvals. The 81 approvals with no labeling for children account for 23% of all pediatric-relevant orphan approvals.

For the other 46 approvals (13% of relevant indications), FDA found some, but not enough, pediatric information. “In general, the incomplete labeling was not specifically related to efficacy or safety data,” FDA said. “Rather, for those indications, the labeling did not address use in specific populations, generally the youngest populations where it would be appropriate to use the indicated drug.”

The FDA working group also looked at clinical development programs for all indications that currently are not fully labeled for pediatric use. For 29 of the 127 indications with missing information, or 23%, the group identified “ongoing studies or that the agency had issued a [written request] for pediatric studies.” FDA can issue written requests to sponsors under the Best Pharmaceuticals for Children Act (BPCA) that outline the studies the agency is requesting; sponsors who “fairly respond” to the WR can earn 6 months of additional marketing exclusivity.

Patching Holes In Incentive Structure

The FDA has long tried to incentivize research and approval of drugs in pediatric patients, with the BPCA and the Pediatric Research Equity Act (PREA) standing as keystones. “Together, BPCA and PREA have led to over 770 prescription product labeling changes to incorporate pediatric-specific information,” according to the pediatric orphan labeling report.

Gaps, of course, remain. FDA noted that BPCA is voluntary. Under PREA, the agency can require sponsors to submit pediatric assessments or, if appropriate, molecularly targeted pediatric cancer investigations “regarding the drug’s safety, effectiveness, dosing, and administration in pediatric populations,” the report explained, but the PREA authority “does not apply to drugs for indications for which orphan designation has been granted.”

While showcasing the “significant number of drugs with orphan designation [that] are appropriately labeled in children,” the report concludes by pointing to work still to be done. “There is a public health need for additional pediatric information in labeling for over one-third of approved orphan indications that are relevant in the pediatric population,” the report states. The FDA pledged to continue to work with stakeholders to “support ensuring that information to support labeling is obtained for all appropriate pediatric age groups.”

 pediatric populations, safety data obtained from pediatric trials for other indications, pharmacokinetic modeling and simulation data, and studies conducted under the Animal Rule.”

The vast majority of the fully labeled approvals – 198 indications, or 90% – “were labeled for use in the full age range of affected pediatric patients at the time of original approval of the product,” the FDA said. The other 23 indications (10%) were not labeled for full pediatric age range in the original approval, but were subsequently supplemented to “extend the indicated population to the full age range of affected pediatric patients.”

“Exclusively pediatric diseases or diseases in which pediatric patients comprised a majority of the overall disease population were most likely to be fully labeled for pediatrics,” FDA concluded. “Conversely, indications for diseases or conditions where pediatric patients were a low percentage of the overall populations were less likely to be fully labeled for pediatrics.”

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But there are strategies that pharmaceutical companies can adopt in emerging markets, the report continues. Developing a local disease management consensus can be an important market-shaping opportunity for industry, and engaging local champions may be critical in very bureaucratic emerging markets.

In some countries, such as Russia, it might be possible to conduct a small Phase IV study to build the value case for a product. Wealthier regions in some emerging markets, such as Moscow or Saint Petersburg in Russia, may be able to add additional products to their local reimbursement listings.

“Inflexible Payer Systems
Developing country health systems often lack the flexibility and resources to implement exceptional reimbursement for orphan drugs. "It is critical for companies to study the marketplace thoroughly before entry, as it cannot be assumed that payers will make allowance for the rarity of the disease and the small size of the target population."

The report notes that donating drugs has only had limited success in emerging markets, as persuading payers to fund a drug that is already available under a patient assistance program may be difficult.

Few emerging markets recognize disease subtypes as rare disorders, an important challenge for oncology drugs with multiple indications, and some tumor types that are considered rare in Western countries are more prevalent in some developing Asian and Latin American markets, such as the prevalence of gastrointestinal stromal tumors (GIST) in some regions in China.

“Market-shaping plans must reflect the lower level of disease awareness, and be sensitive to the differing evidence needs of emerging markets, where hard outcomes and clear value messaging around costs and benefits resonate best,” the report says.

However, companies must be mindful of complying with local rules on interacting with clinicians, intruding in the diagnostic process and conducting local clinical studies, the DM report warns. In some developing countries, companies are obligated to fund lifelong treatment for any patient that receives an orphan drug within a clinical trial. In some circumstances, pharmaceutical companies have funded the genetic testing for rare disease in some emerging markets, but that approach has not been without controversy.

Made In China Gene Therapy: A Father’s Quest To Save Son With Ultra-Rare Condition
A JOURNEY TOWARDS GENE THERAPY FOR ULTRA-RARE DISEASES IN CHINA

BY BRIAN YANG

When Jian Shu’s son Yue first started walking, he noticed that there was something not quite right, as the baby boy seemingly could not keep his body in balance.

Jian took Yue, whose name means happiness in Chinese, to see a doctor, who could not find what was wrong so ordered a gene sequencing test. The result showed that Yue had a type of progressive muscular dystrophy, a rare genetic condition that is usually inherited from a female carrier. But this was puzzling for Jian because when both he and his wife had gene testing they were found not to carry the gene that causes the condition. The reason why their son had dystrophy remained a mystery.

The most common form of muscular dystrophy, Duchenne muscular dystrophy (DMD) affects roughly one in 3,500 newborns, mostly boys. Symptoms start to show from age two and as the condition progresses, most boys have weaker muscular function compared with their peers and by 12 years old they usually lose the ability to walk. Most DMD sufferers die by the age of 20 to 30 due to respiratory function or heart failure.

There was no available treatment for DMD until 2016, when the US FDA approved Sarepta Therapeutics Inc.’s Exondys 51 (eteplirsen) for patients with the exon 51 skipping gene mutation. Later, another drug Imflaza (deflazacort), developed by Marathon Pharmaceuticals LLC

Patient-driven drug development meets the old saying of “where there’s a will, there’s a way” in China, potentially the world’s largest market for rare disease treatments.
oversight systems. For hospitals, the National Health
develop therapies, but under two separate regulatory
both qualified hospitals and biopharma firms can
be a clear and well-defined regulatory pathway, a
This journey will not be easy. Firstly, there needs to
learned about a company in Beijing developing
Official: Novartis SMA Gene Therapy Zolgensma Is
of $2.1m for the one-time treatment.
backed by Novartis last year for $8.7bn, it was
This May, a breakthrough for gene therapy in
vector company, FivePlus Molecular
Back in China, when Yue's condition progressed,
metabolic came when the US FDA granted the green
light to Novartis AG's Zolgensma (onasemnogene
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on the development of vectors, which carry and
deliver re-engineered genes back into a patient's
body. Not long after it started developing an adeno-
associated virus (AAV), FivePlus began collaborating
with a physician in Wuhan-based Tongji Hospital,
a top Class AAA facility in China's central
metropolitan area. An eye doctor named Bin Li had
specifically asked the company to develop a vector
for an experimental study treating patients with
Leber's hereditary optic neuropathy.
FivePlus was developing various vectors and AAV
had shown superiority due to its safety profile.
Physician Li came knocking on the door with the
ease for any gene or cell therapy to get approved
and launched in any given market. In China, there is
currently a confusing “two-track mechanism”
for such emerging technologies. This means that
both qualified hospitals and biopharma firms can
develop therapies, but under two separate regulatory
oversight systems. For hospitals, the National Health
Commission now oversees all matters governing how
such products are developed. The National Medical
Products Administration issues rules on how drug
companies can develop cell and gene products.

The confusing system has industry regulatory
professionals worried that it will lead to lowered
quality, redundant costs and wasted investment.
Currently, developers of proposing cell therapies
to treat blood cancers or rare conditions need
to go through the National Medical Products
Administration (NMPA, formerly the China FDA) to
get an IND before starting a clinical study. Although
there is a 60-day time frame for such applications, if
a sponsor hears nothing back from the regulator it can
go ahead with the study.

The Beijing vector company, FivePlus Molecular
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both qualified hospitals and biopharma firms can
develop therapies, but under two separate regulatory
oversight systems. For hospitals, the National Health
Commission now oversees all matters governing how
clinical trial,” noted a research paper summarizing
the study published in EbioMedicine in August 2016.
The encouraging results gave FivePlus founder
Xiaoyan Dong confidence to take on the case of
Jian's son, who turned out to have a condition so
rare that the diagnosis took a toll on the family and
the father's quest to find a cure.

In 2016, gene therapy and its clinical use again
entered Chinese researchers' consciousness when the
Western China Hospital in Chengdu started
the world's first CRISPR gene editing experiment in
humans, treating lung cancer patients.

One in 10 Million
When Jian took Yue to visit FivePlus' office in Etown,
a suburb of Beijing, his son was finally diagnosed
with Emery-Dreifuss muscular dystrophy (EDMD),
one of nine forms of muscular dystrophy. The
diagnosis came after multiple trips to physicians
and rounds of tests. Soon after taking on the case,
FivePlus researchers started a primary document
review on EDMD and related potential treatment
opportunities. In the meantime, the boy's whole gene
sequencing results were sent out to other medical
specialists in muscular dystrophies both inside
and outside China.

After further and closer examination, Yue was
eventually found specifically to have reducing body
myopathy (RBM) with FHL1 mutation. If EDMD is a
rare muscular dystrophy, RBM is so rare that there
are few known cases around the world. After the
diagnosis, Jian combed China to find other patients,
and so far has found two other families with
sufferers. In the US, the total known number of
RBM cases is reported to be in the 30s, putting the
occurrence rate at roughly one in 10 million.

Help From US Facilities
Due to its ultra-rare nature, RBM has attracted the
tention of very few researchers around the world,
posing an additional challenge to FivePlus researchers
scouting for an animal model. Of two prospects they
have found, only one has given them some hope. The
Ju Chen Lab at the University of California San Diego
(UCSD) was one of the places in the world conducting
preclinical research on RBM with the FHL1 mutation.
Professor Chen, upon being approached by the
FivePlus Beijing team, agreed to provide rats from the
lab for FivePlus to conduct the research.

After rounds of email communications and a
payment to the school for the animals, a batch
of FHL1 gene knockout mice generated in the US
laboratory started their journey to China's capital.

Other than the UCSF team, the handful of
physicians globally specialized in RBM included
Carsten Bonnemann at the Philadelphia Children's
Hospital in Pennsylvania, who spends part of
his time conducting research at the National
Institutes of Health in Bethesda, MD. With slim
hope, Jian decided to seek out Bonnemann's help
in diagnosing and treating his son, the determined
father undaunted by the huge distance between
Hangzhou and Philadelphia.

Working a job at a large national grocery chain
in China, Jian had an insurance policy with China
Pingan Insurance Co., which luckily covered his trip
to seek medical help overseas. After days of back-
and-forth arrangements, Jian embarked on the long-
sought journey to take Yue to see Bonnemann.
Again, the diagnosis was confirmed. “The mutation
that was found is very convincing for this diagnosis
and I have no doubt that it's correct,” noted the
physician. But the diagnosis also came with feelings
of hopelessness. “It is very important that the
family understand that sadly there currently are no
treatments for this disease, in other words, even
here at NIH there is no clinical treatment trial for
reducing body myopathy,” the physician stressed.

But the effective sentence of “no cure, no hope” from
one of the most authoritative voices on RBM still did
not deter Jian, who by then had signed on FivePlus to

test an experimental gene therapy for an ultra-rare condition for which even the world’s most prestigious research institute had no previous experience.

**Research Setback**

Months after the November day when Jian came to FivePlus and signed the research agreement, the batch of RBM rats from UCSD arrived in China. After one month of quarantine and rounds of blood tests, the animals finally arrived at the company’s lab.

According to a research paper published by the UCSD team, the rats need to reproduce to ensure sufficient numbers to perform studies, but in China there were nowhere to find suitable mates, so alternatives had to be found. Soon the number of RBM rats expanded to dozens, but strangely they did not develop the condition and die within a certain period as planned. Later research also confirmed the rats failed to develop RBM.

The unexpected results had researchers puzzled, so they started communicating with the UCSD team about the results but no real progress was made. The experimental work thus came to an abrupt halt in June. Seeing no path forward, FivePlus decided to end the project pending a new approach to salvage it. Facing a backlash, the Beijing company reconsidered its decision to tackle some ultra-rare conditions, despite the early success with hereditary optic neuropathy.

For Yue’s condition, his particular mutation has its own challenges. There are distinct splice variants of FHL1, namely FHL1A, FHL1B and FHL1C and the boy’s mutation was found to lie in between the variants.

**General Challenges**

More generally, gene therapy itself remains a complicated process. The eagerness to develop breakthrough technology and to be recognized as a global pioneer among many young Chinese researchers has also caused some concern over the speed and ethical practices involved in gene therapy and editing research in the country.

Last November, Jiankui He from the Shenzhen-based Nanhun Institute of Technology shocked the world with an announcement of the birth of the world’s first gene-edited babies. Amid a global outcry over the lack of sufficient ethical clearances and peer reviews, China significantly tightened oversight of gene research studies. (Also see “China Tightens Clinical Trial Oversight Post Gene-Edited Babies Scandal” - Pink Sheet, Feb 28, 2019.)

Gene therapy is not simply a drug product but is more akin to a surgical process, noted Xiaobing Wu, founder of the FivePlus-associated Ruixi Gene Technology Research Institute. One of Ruixi’s early backers included the mother of a young girl with Sanphillippo syndrome, and since then the institute has taken on spinal muscular atrophy and other rare neuromuscular conditions.

Many uncertainties still surround gene therapy as an emerging treatment modality, and researchers and patients must prepare for these.

**Hope Remains For Yue**

NIH researcher Bonnemann agreed that for RBM research further studies to gain a better understanding of the disease's mechanism may be the best way forward. “We are currently trying to understand the ‘natural history’ of the disease and investigate the MRI [magnetic resonance imaging] appearance of the disease, but again, sadly at this time we have no treatment to offer,” noted the specialist.

However, Jian is refusing to throw in the towel just yet, and said he was in discussions with other researchers to find a new gene therapy to treat his son’s condition. Despite the setbacks, being told there is no cure by a medical expert and facing large out-of-pocket expenses, the father said he had no regrets. His quest to find a cure for his son lives on.

**Pricing**

Priced at $125,000 per injection and $750,000 for the first year of treatment, Biogen Inc’s Spinraza (nusinersen) is the first US FDA-approved treatment for rare spinal muscular atrophy (SMA), and now the company is looking to bring the high-priced drug to China.

Riding the country’s surging wave of new therapies and accelerated approvals for critical and rare disease treatments, the US biotech has unveiled ambitious plans including setting up local operations, hiring medical affairs talent, and actively engaging physicians and patients.

So far, the regulatory process seems to be going well. Biogen’s new drug application (NDA) has been accepted by China’s National Medical Products Administration (NMPA, formerly the CFDA), using the agency’s conditional approval pathway and acceptance of clinical data obtained outside China. Issued in July, the policy is viewed as a major step forward to expedite the entry of innovative new drugs into the world’s second-largest pharma market. For therapies for rare diseases, pediatric use or critical conditions such as cancer, drugmakers can now use the overseas clinical data directly toward an NDA in China, although a postmarketing study may be required. (Also see “Rare Diseases: What Makes China A Rising Star?” - Pink Sheet, Sep 26, 2018.)
More cities are starting to offer local coverage for orphan drugs. For instance, Tianjin recently issued partial coverage of Sanofi’s Myozyme (alglucosidase alfa) for Pompeo disease. The scheme provides 70% reimbursement for patients using five vials of the injection drug, 60% for expenses of six to 10 vials and 50% for up to 15 vials of usage, with no coverage above 15 vials. After the initial coverage, low-income patients can still apply for financial aid if they meet certain criteria.

Orphan drug makers are hoping that more cities will follow the lead of Qingdao and Tianjin and provide coverage for orphan drugs.

**Government Coverage: A Long Short?**

Although China’s National Health Commission has released the first official national Rare Conditions List containing 121 diseases, the government has not yet disclosed plans to cover the treatment costs for these conditions.

Some hope that the country’s new Medical Insurance and Support Administration will start covering orphan drugs, after the agency’s first major move to provide coverage for 17 anticancers, after behind-the-door negotiations and deep price concessions from companies, the majority of which are multinationals.

Compared with treatments for life-threatening cancers, rare diseases affect a much smaller population, and some orphan drugs are similar or even costlier than their oncology counterparts. The prospects of expanded coverage for orphan drugs using a similar price negotiation mechanism is still uncertain.

**PAP Power**

Despite the local coverage provided in Qingdao and Tianjin, rare disease treatment remains largely a private-pay market. To expand access, many multinational drugmakers are now offering patient assistance programs (PAPs).

Bayer AG started its PAP for MS drug Betaferon (interferon beta-1b) in 2012, when the German firm partnered with China Charity Federation and launched the “3+9” program, in which patients pay for the first three months of treatment, and then get free drugs for the next nine months. Priced at CNY850 per injection, a MS patient needs 15 injections per month, amounting to 180 injections in a year totaling CNY153,000.

With the PAP, a MS patient on Betaferon would pay CNY38,250, around a quarter of the normal cost.

In July, another European drugmaker, Sanofi, obtained approval for its MS drug Aubagio (teriflunomide), and the French company is also set to launch a PAP in China. Priced at CNY12,500 for a box of 28 x 14mg tablets, the PAP provides low-income patients with certain assistance. For first-time applicants, after purchasing four boxes, the company provides two boxes free of charge; and for repeat applicants, a three-box purchase means three boxes free.

With the PAP, the monthly cost becomes CNY7,921, compared with CNY13,393 without it.

**Post-PAP Shortages?**

After five years of its PAP, Bayer finally obtained long-awaited official reimbursement coverage for Betaferon in 2017, but soon supplies began running out even in some top-rated Chinese hospitals.

Last July, Betaferon was one of two rare disease treatments that were included in the China’s National Reimbursement Drug List, with a negotiated price of CNY590 per dose. Out-patients can get 85% of the cost reimbursed.

Following the coverage, Bayer ended the PAP from 2018.

This September, however, many MS patients reported that many hospitals in Beijing, including top-ranked Class 3A facilities, had run out of Betaferon and that patients were having to self-pay for the drug from retail pharmacies.

One major reason was the “global budget control” system adopted by hospitals to limit the prescribing of high-cost drugs. Under the scheme, hospitals are required to bring down drug costs to under 30% of total expenditures, but the use of higher-cost drugs has made this goal harder to achieve.
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