MM&M THERAPEUTIC FOCUS

Rare Diseases

The rare disease drug market is making history with its steady growth and burgeoning pipeline—and owing to continuing breakthroughs in gene therapy, the biggest advances are yet to come. **Rebecca Mayer Knutsen** reports on a sector that's thriving—and on the possibility that issues around pricing can slow its surge

Currently on the cusp of a seismic shift toward innovative, ultra-targeted therapeutics, the rare disease market continues to be dominated by small-molecule medications. Industry analysts have focused their thoughts on a future full of promising gene therapy, immunotherapy and biologic products. In the orphan medication market, Alexion Pharmaceuticals, Vertex Pharmaceuticals and NPS Pharmaceuticals have potential blockbuster drugs waiting in the 2015 approval wings for the treatment of hypophosphatasia, cystic fibrosis and hypoparathyroidism.

"We're entering the golden age of orphan drugs," says Chris Clark, co-portfolio manager at RS Investments. "In the next three to five years the industry will usher in many successful drugs that will eradicate diseases. Our children won't know the diseases we knew growing up."

By 2020, orphan drugs will own 19% of the total share of prescription drug sales excluding generics, reaching a whopping $176 billion in annual sales, according to Andreas Hadjivasiliou, an analyst with EvaluatePharma. Developed to treat patient populations of fewer than 200,000 patients, orphan drugs generate large per-patient payments, fueling a raging debate in the industry. The category has attracted the attention of insurers, who will be looking to stifle cost growth as more drugs hit the market.

Unmet medical needs and understanding the biology of a targeted therapy for subset populations claim the limelight, says Jeffrey Bacha, chairman, president and CEO/cofounder of Del Mar Pharmaceuticals, which is developing VAL-083 for glioblastoma multiforme, the most aggressive form of brain cancer. Similarly, Timothy Coté, MD, principal and CEO of Coté Orphan, believes the future is now for gene therapy. He expects a product to gain approval in this category by 2016, at the latest.

By introducing genes into the body to treat diseases, gene therapy might hold the key to curing many rare diseases. But the cost question will present challenges. All eyes were on Dutch biotech company UniQure when the price of the first gene therapy—a potential one-time curative treatment—was set at $1.4 million in Germany, shattering the global record for a rare disease medicine. UniQure's Glybera was approved in the European Union to treat lipoprotein lipase deficiency.

Celladon was granted breakthrough therapy designation by the FDA for its cardiovascular gene therapy Mydicar in April 2014. The gene therapy was developed to boost production of an enzyme known as SERCA2a, which plays a key role in recycling calcium in the heart's muscle cells.

Coté believes gene therapy has the potential to be lucrative but warns of the tremendous challenges the industry faces in the interim. "A lot is on the line," he says. "When the hope for a complete cure isn't realized, then what happens?"

The Pricing Game

Big pharma has its sights set on the rare disease market—for good reason: Orphan drugs are positioned to offset the mount-

TOP 25 RARE DISEASE PRODUCTS

Category leaders, ranked by 2014 global sales, and their US media spend

Rank	Product	Manufacturer	Global sales $ (millions)	Vs. prior 12 mos.	US DTC media $ (000s)*	Vs. prior 12 mos.	US journal media $ (000s)*	Vs. prior 12 mos.
1	**Rituxan**	Roche	$7,635.0	2.0%	$0.7	N/A	$0.0	N/A
2	**Revlimid**	Celgene	$4,980.0	16.0%	$0.0	N/A	$1,820.0	81.7%
3	**Gleevec**	Novartis	$4,695.0	0.0%	$0.0	N/A	$0.0	N/A
4	**Copaxone**	Teva	$3,810.0	-12.0%	$0.0	N/A	$1,025.0	36.2%
5	**Avonex**	Biogen Idec	$3,019.0	N/A	$0.0	N/A	$82.0	-90.9%
6	**Alimta**	Eli Lilly	$2,810.0	4.0%	$0.0	N/A	$1,246.0	78.4%
7	**Rebif**	Merck KGaA	$2,414.0	-3.0%	$0.0	N/A	$0.0	N/A
8	**Soliris**	Alexion	$2,225.0	43.0%	$0.0	N/A	$14.0	-96.7%
9	**Advate**	Baxter	$2,083.0	6.0%	$0.0	N/A	$142.0	-26.5%
10	**Velcade**	Takeda/J&J	$1,766.0	6.0%	$0.0	N/A	$0.0	N/A
11	**Sandostatin LAR Depot**	Novartis	$1,657.0	4.0%	$0.0	N/A	$94.0	100%
12	**Tracleer**	Actelion	$1,649.0	N/A	$0.0	N/A	$0.0	N/A
13	**NovoSeven/NovoSeven RT**	Novo Nordisk	$1,636.0	-1.0%	$0.0	N/A	$214.0	14.5%
14	**Afinitor**	Novartis	$1,567.0	20.0%	$0.0	N/A	$2,373.0	-6.1%
15	**Sprycel**	Bristol-Myers Squibb	$1,520.0	19.0%	$0.0	N/A	$367.0	100%
16	**Tasigna**	Novartis	$1,511.0	19.0%	$0.0	N/A	$0.0	N/A
17	**Kogenate**	Bayer	$1,440.0	-10.0%	$0.0	N/A	$115.0	N/A
18	**Yervoy**	Bristol-Myers Squibb	$1,285.0	34.0%	$0.0	N/A	$757.0	100%
19	**Velcade**	Takeda	$1,193.0	-28.0%	$0.0	N/A	$320.0	-29.6%
20	**Sutent**	Pfizer	$1,183.0	-2.0%	$0.0	N/A	$21.0	-88.4%
21	**Sensipar**	Amgen	$1,154.0	6.0%	$0.0	N/A	$0.0	N/A
22	**Norditropin SimpleXx**	Novo Nordisk	$1,148.0	5.0%	$0.0	N/A	$0.0	N/A
23	**Betaseron**	Bayer	$1,128.0	-18.0%	$0.0	N/A	$0.0	N/A
24	**Nexavar**	Bayer	$1,026.0	N/A	$0.0	N/A	$237.0	N/A
25	**Cerezyme**	Sanofi	$954.0	4.0%	$0.0	N/A	$0.0	N/A

*Media spend for the 12 months ending Sept. 30, 2014 (DTC), and ending Nov. 30, 2014 (journal)

Sources: Sales, EvaluatePharma; DTC media spend, Nielsen; journals, Kantar Media

ing pressure of blockbuster drugs faced with patent expirations. Industry experts expect the patent cliff to continue sending waves through revenue streams into 2016.

Novartis, Abbott, GlaxoSmithKline and others are turning to orphan drug opportunities to line up future revenue sources. "Their interest validates the smaller companies that are making investments in R&D," Clark notes. "The most successful orphan drugs require commercial investment and the developers are too small to carry them for the long haul."

According to Coté, parties on either side of the equation need one another. "The movers and shakers are scrappy little endeavors," says Coté. "They're willing to put everything on the line and make quick decisions. Big pharma's culture doesn't allow high-risk innovation."

Orphan drug legislation provides various incentives to encourage companies to develop drugs with better efficacy for unmet medical conditions, explains Bhanu Shankar Singh, senior analyst at Technavio. The 1983 Orphan Drug Act altered the market and opened its doors for the orphan drug deluge.

The biggest issue at play is the high cost of producing an orphan drug. The number of patients eligible to receive an orphan drug limits a company's ability to recoup its R&D investment, says Edward Buthusiem, managing director, Berkeley Research Group. "Manufacturers need incentives to cover the high cost of development," he explains. "It's a narrow market and profit is based on supply and demand. By order of magnitude, these drugs are more expensive."

Last year, the average annual orphan drug cost per patient was $137,782, compared with an average of $20,875 for a non-orphan drug, Hadjivasiliou reports. "The media has turned its attention to what is viewed as extreme pricing," acknowledges Bacha. "High costs drive the ability to make the investment in therapy. The political landscape is evolving so we'll see how it shakes out."

The Department of Health and Human Services is threatening the current price structure with its rule that permits healthcare organizations and certain designated entities to purchase orphan drugs at 340B discounted prices but only if the drug is used to treat conditions other than the rare disease for which the drug received its orphan designation. The fight continues into 2015, with opposition from the Pharmaceutical Research and Manufacturers of America.

Drugmakers, too, are up in arms about preventing physicians from writing a script for the less expensive indication. "The pricing controversy creates a disincentive for manufacturers to seek non-orphan uses for their orphan drugs," notes Buthusiem.

A Look Back

Of the 44 rare disease drugs approved by the FDA in 2014, major new advances included Eloctate, the antihemophilic factor (recombinant) Fc fusion protein for hemophilia A from Biogen Idec, and Cerdelga (eliglustat) for Gaucher disease type 1 from Genzyme. The industry witnessed successful product launches to treat lysosomal storage disorder Morquio A syndrome (BioMarin's Vimizim); metabolic disease generalized lipodystrophy (Aegerion Pharmaceuticals' Myalept); and genetic condition hereditary angioedema (Salix Pharmaceuticals' Ruconest).

Clark proclaims BioMarin the success story of 2014. In the year ahead, the developer will rake in revenue thanks to expanded sales of its enzyme-replacement therapy Vimizim.

CLINICAL CORNER

With potential to crush the projected $4-billion mark in revenue, the combination cystic fibrosis (CF) drug VX-809 (lumacaftor) and Kalydeco (ivacaftor) create quite a buzz among industry analysts, investors and drugmakers.

Vertex Pharmaceuticals submitted a New Drug Application to the FDA for its combination product to treat the 22,000 people ages 12 and older who have two copies of F508del, the most common CF mutation.

"In CF, abnormal chloride transport across the body's cellular membranes results in thickened secretions that severely impact airways, liver, pancreas, GI tract and reproductive function," explains Mike Hodgson, partner and chief creative officer, Cambridge BioMarketing.


Chris Clark

People with two copies of the F508del mutation lose nearly 2% of lung function every year. To date, all medicines have addressed the symptoms of the disease but not its underlying cause—the defective Cystic Fibrosis Transmembrane Conductance Regulators (CFTR) protein. According to Technavio senior analyst Bhanu Shankar Singh, the drug combination is designed to hydrate and clear mucus from the airways. Lumacaftor addresses the processing and trafficking defect of the F508del CFTR protein to enable it to reach the cell surface where ivacaftor helps the CFTR channel at the cell surface open more often to improve the transport of salt and water across the cells, he explains.

"Vertex is the first company to get to the root of CF," adds Timothy Coté, MD, principal and CEO of Coté Orphan. "Until now, drugs were simply supportive care."

Market Potential

As for the market potential of Vertex's combination product, EvaluatePharma analyst Andreas Hadjivasiliou says that it has "a NPV that is considerably higher than the next product. This suggests the market has high hopes and expects the product to be a significant revenue driver."

Chris Clark, co-portfolio manager at RS Investments, believes the drug may hit the $5-billion mark fairly rapidly. He predicts revenue of as much as $1 billion in the drug's first full year and potentially $5 billion during the next three to five years.

Ivacaftor has shown remarkable growth as a monotherapy. Its revenue nearly doubled, from $171 million in 2012 to $371 million in 2013, Singh reports. Factors that may support or inhibit its growth, he says, include its potential to offer a meaningful clinical benefit for vast majority of CF patients; lengthy patent expiration dates and potential expansions; a dry pipeline; and the potential for breakthrough therapy status.

"The combo approach is of great interest in the industry, and Vertex's strategy has been successful because it makes good scientific sense," Coté observes. Phase-III study results showed improvement in lung function and other key markers of disease. Vertex is conducting a trial in younger patients during the first half of 2015. For patients with one copy of the F508del mutation, Vertex is conducting an eight-week Phase-II trial, according to Hodgson, who worked on one of the original targeted CF therapies, Pulmozyme from Genentech, in the mid-1990s.

"Astounding medical advances have changed the outlook for these patients and families," Coté explains. "We're witnessing how powerful medicine is becoming as we combine our understanding of genetics, immunology, and new approaches to drug discovery."

In an unprecedented move, BioMarin sold its priority review voucher, awarded by the FDA for Vimizim last February, to Sanofi and Regeneron for $67.5 million just five months later. Designated for tropical and pediatric rare diseases, the priority review vouchers are a new incentive to spur the development of products for rare diseases and may be sold or transferred an unlimited number of times.

"Naysayers said the program wasn't going to work," Coté says. "But 2014 was a big year for this process. These incentives turned out to be highly valuable." And acquisitions emerged as an important part of the landscape in 2014. Roche acquired InterMune and BioMarin acquired Prosensa Holding N.V. and its rare disease candidate drisapersen for Duchenne muscular dystrophy (DMD). "This is a big move in the industry in a high-profile area," says Clark, who believes drisapersen has a good chance of gaining approval mid-2015.

According to Coté, the orphan exclusivity battle that Depomed entered into—and won—against the FDA in 2014 was an important breakthrough. The court awarded Depomed orphan drug exclusivity for its postherpetic neuralgia drug Gralise. Other products that gained approval in 2014: Merck's Keytruda (pembrolizumab) for advanced or unresectable melanoma, and Boehringer Ingelheim's Ofev (nintedanib) for idiopathic pulmonary fibrosis (IPF). Two drugs emerged in the cystic fibrosis space: Vertex Pharmaceuticals' Kalydeco (ivacaftor) and Pharmaxis Pharmaceuticals' Mannitol.

What to Expect in 2015 and Beyond

Cambridge BioMarketing's Mike Hodgson notes optimistically that a number of promising compounds ranging from breakthrough oncologic advances to ultra-orphan therapies are in late-stage clinical trials. Compounds of great interest are asfotase alfa from Alexion, Intercept Pharmaceuticals' obeticholic acid (OCA) and sebelipase alfa from Synageva BioPharma.

Alexion will continue to dominate sales in the sector. Soliris (eculizumab) has been approved for aHUS, a rare blood condition causing kidney failure. Once approved, the enzyme-replacement therapy asfotase alfa is expected to net high profits, Clark says. It has been granted orphan drug status in Japan and Alexion submitted a Biologics License Application to the FDA in December.

Bacha believes immunotherapies will make a much-needed mark on oncology in the next few years. "The attention is on unlocking our immune systems to assist in the treatment of cancer," he explains.

Armed with cancer immunotherapeutic Opdivo, Bristol-Myers Squibb is expected to unseat market leader Novartis in 2020, reports Hadjivasiliou. In addition to Keytruda, 2014 oncology advances included trametinib and dabrafenib, GlaxoSmithKline's combo product under development for melanoma; eltrombopag for aplastic anemia, also from GSK; and Avastin for ovarian cancer. Imbruvica (ibrutinib), manufactured by Pharmacyclics, was approved for the rare blood and bone marrow disease chronic lymphocytic leukemia (CLL). Gilead Sciences' Zydelig is the fifth new drug with breakthrough therapy designation to be approved by the FDA and the third drug with this designation approved to treat CLL.

Other early-stage orphan drugs to keep an eye on, according to Singh, include PTC Therapeutics' Ataluren (translarna) for cystic fibrosis, Vertex Pharmaceuticals' cystic fibrosis compound VX-661, Genentech's Actemra (tocilizumab) for the treatment of systemic sclerosis, Catalyst Pharmaceutical's Firdapse (amifampridine) to address Lambert-Eaton myasthenic syndrome and Millennium Pharmaceuticals' osteosarcoma drug Mifamurtide. ■