Rare Diseases

"New and improved" has entered this space. Alongside the existing compounds that are transforming the lives of patients with orphan ailments, a wave of incrementally better products is coming out. **Noah Pines** reviews the significant rare-disease market trends

Orphan Drugs 2.0 has arrived. Manufacturers in this space are evolving their business models, from offering life-saving therapies to making available treatments that boost patient quality of life, as they seek to further normalize the lives of people living with rare diseases.

Over the past 30 years, thanks in part to government incentives and other measures, treatment options for patients with many ultra-rare and severe, life-threatening diseases—patients who without these therapies had no other hope—have multiplied. Today about 300 of the roughly 7,000 identified rare diseases have treatments.

Many such therapies have become commercially successful. Worldwide sales for the top 50 orphan brands rose by 9% in 2012 to $69.9 billion, according to data from market research firm EvaluatePharma.

Recently, there has been a bifurcation into two different segments of new drug candidates: those which are innovators, and those which are better orphans. "We are seeing more and more drugs coming to market that are improvements over those which exist," says Tim Cote, MD, MPH, former director of FDA's Office of Orphan Products Development and now an industry consultant.

One example is Actelion's Opsumit (macitentan), approved in October for pulmonary arterial hypertension (PAH), a chronic, progressive and debilitating disease that can lead to death or the need for lung transplantation. Patients on Opsumit don't have to be monitored for liver safety, an advance over Actelion's earlier PAH drug, Tracleer (bosentan).

While few alternatives for PAH existed a decade ago, today the treatment arsenal has become crowded. Two other drugs for pulmonary disorders recently scored approval, Bayer's Adempas (riociguat) and United Therapeutics's Orenitram, an oral form of the drug Remodulin (treprostinil). The new PAH drugs also compete against Gilead's Letairis (ambrisentan) and Pfizer's Revatio (sildenafil).

Newer meds like Opsumit aim to not only lengthen patients' lives, but also to help sufferers manage the ailment more easily. Among the orphan drugs available, many are "rather good at saving people lives," says Mike Hodgson, partner and chief creative officer, Cambridge BioMarketing. "What's next is to help them live as normally as they possibly can."

The orphan-better trend got a push from provisions that if a product is clinically superior (i.e., more effective, safer or a major contribution to patient care), it can receive orphan designation, says Cote. The completely innovative compounds, he says, are now "going forward right alongside this secondary market trend of products that are...the same moiety, the same API, as the innovator, but different in such a way that [they] meet clinical superiority criteria."

Highly engaged patient communities are also supporting development of these meds, as they have for other rare-disease drugs (see sidebar). "These patients are able to articulate the true value of these treatments," says Peter Nalen, president/CEO of Compass Healthcare Marketers. "A drug taken twice a day vs. four times a day can be a meaningful difference, so that the parent who needs to administer it to their child can actually sleep through the night. That is a real value to a mom, a dad or a kid, but that often does not get looked at in the clinical trials."

An example is Raptor's enteric-coated Procysbi (cysteamine bitartrate), for nephropathic cystinosis, approved in 2013. An immediate-release tablet, Mylan's Cystagon, was approved in 1994. Procysbi is a long-acting form that also offers fewer AEs than the initiator compound.

TOP 50 RARE DISEASE PRODUCTS

Category leaders, ranked by 2012 global sales, and their US media spend

Rank	Product	Manufacturer	US 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	$7,155.3	5.4%	$414.3	-12.2%	$0.0	N/A
2	**Gleevec**	Novartis	$4,675.0	0.3%	$0.0	N/A	$0.0	-100.0%
3	**Neulasta**	Amgen	$4,092.0	3.5%	$802.3	>100.0%	$586.2	14.8%
4	**Copaxone**	Teva	$3,996.0	34.4%	$0.0	N/A	$0.0	N/A
5	**Revlimid**	Celgene	$3,766.6	17.4%	$0.0	N/A	$1,001.7	N/A
6	**Avonex**	Biogen Idec	$2,913.1	8.4%	$369.7	>100.0%	$900.0	2.9%
7	**Alimta**	Eli Lilly	$2,594.3	5.4%	$6.1	-4.0%	$698.5	>100.0%
8	**Rebif**	Merck KGaA	$2,433.4	3.4%	$3.2	84.0%	$0.0	-100.0%
9	**Advate**	Baxter International	$2,074.5	5.8%	$0.0	N/A	$193.5	9.8%
10	**Tracleer**	Actelion	$1,600.5	-7.0%	$0.0	N/A	$0.0	-100.0%
11	**Betaseron**	Bayer	$1,563.5	0.6%	$0.0	N/A	$0.0	-100.0%
12	**NovoSeven**	Novo Nordisk	$1,543.0	-1.0%	$0.0	N/A	$187.2	23.8%
13	**Kogenate**	Bayer	$1,519.8	1.6%	$0.0	N/A	$0.0	N/A
14	**Sandostatin LAR**	Novartis	$1,512.0	4.8%	$2.5	>100.0%	$63.9	-28.0%
15	**Velcade**	Johnson & Johnson	$1,500.0	17.7%	$0.0	N/A	$454.6	-71.5%
16	**Zometa**	Novartis	$1,288.0	-13.4%	$13.9	-53.0%	$467.8	-52.2%
17	**Neupogen**	Amgen	$1,260.0	0.0%	$0.0	N/A	$0.0	N/A
18	**Sutent**	Pfizer	$1,236.0	4.1%	$0.8	-74.0%	$181.1	-39.4%
19	**Soliris**	Alexion	$1,134.1	44.8%	$0.0	N/A	$413.9	84.6%
20	**Sprycel**	Bristol-Myers Squibb	$1,019.0	26.9%	$5.5	-69.0%	$379.8	-39.3%
21	**Nexavar**	Bayer	$1,018.3	0.9%	$0.2	-68.0%	$0.0	N/A
22	**Tasigna**	Novartis	$998.0	39.4%	$0.0	-100.0%	$35.0	-97.3%
23	**Norditropin SimpleXx**	Novo Nordisk	$984.2	4.4%	$64.5	>100.0%	$0.0	N/A
24	**Sensipar**	Amgen	$950.0	17.6%	$0.0	N/A	$0.0	-100.0%
25	**Lidoderm**	Endo Health	$947.7	14.8%	$32.4	-81.0%	$0.0	-100.0%
26	**Temodar**	Merck & Co	$917.0	-1.9%	$0.0	N/A	$0.0	-100.0%
27	**Velcade**	Takeda	$881.9	19.8%	$0.0	N/A	$0.0	N/A
28	**Exjade**	Novartis	$870.0	2.4%	$0.0	N/A	$0.0	N/A
29	**Genotropin**	Pfizer	$832.0	-6.4%	$0.0	N/A	$0.0	N/A
30	**Vidaza**	Celgene	$823.2	16.7%	$0.0	N/A	$0.0	N/A
31	**Cerezyme**	Sanofi	$813.9	32.6%	$0.0	N/A	$0.0	N/A
32	**Afinitor**	Novartis	$797.0	79.9%	$2.2	-66.0%	$2,496.2	>100.0%
33	**BeneFIX**	Pfizer	$775.0	11.8%	$0.0	N/A	$61.0	-33.9%
34	**Yervoy**	Bristol-Myers Squibb	$706.0	96.1%	$1.7	>100.0%	$133.9	-86.9%
35	**Valcyte**	Roche	$680.6	5.8%	$0.0	N/A	$0.0	N/A
36	**Suboxone**	Reckitt Benckiser	$646.1	-21.5%	$1,227.9	>100.0%	$176.6	N/A
37	**Treanda**	Teva	$608.0	>100.0%	$0.6	>100.0%	$914.7	-33.9%
38	**Humate P**	CSL	$605.2	2.2%	$0.0	N/A	$0.0	N/A
39	**Myozyme**	Sanofi	$594.0	38.6%	$0.0	N/A	$0.0	N/A
40	**ReFacto AF/Xyntha**	Pfizer	$584.0	15.4%	$0.0	-100.0%	$0.0	N/A
41	**FEIBA VH**	Baxter International	$575.3	2.9%	$0.0	N/A	$0.0	-100.0%
42	**Pulmozyme**	Roche	$572.9	3.0%	$0.0	N/A	$0.0	N/A
43	**Revatio**	Pfizer	$534.0	-0.2%	$0.0	N/A	$0.0	N/A
44	**Elaprase**	Shire	$497.6	7.0%	$0.0	N/A	$0.0	N/A
45	**Replagal**	Shire	$497.5	4.7%	$0.0	N/A	$0.0	N/A
46	**Helixate**	CSL	$485.2	-3.4%	$0.0	-100.0%	$0.0	N/A
47	**Remodulin**	United Therapeutics	$458.0	6.5%	$0.0	N/A	$0.0	N/A
48	**Epadel**	Mochida	$450.0	-6.8%	$0.0	N/A	$0.0	N/A
49	**Teysuno**	Otsuka Holdings	$447.6	-3.2%	$0.0	N/A	$0.0	N/A
50	**Prolastin-C A1P1**	Grifols	$426.8	71.0%	$0.0	N/A	$98.8	N/A

Sales, EvaluatePharma; DTC media spend, Nielsen; journals, Kantar Media. * US media spend for 2012 (DTC) and for the 12 mos. ending Nov. 30 (journals)
Note: Top 50 list excludes generics

CLINICAL CORNER

Among the biggest stories in the latest wave of orphan-disease drug development has been the hunt for a disease-modifying therapy for Duchenne muscular dystrophy (DMD). Two molecules are under investigation, eteplirsen from Sarepta Therapeutics and drisapersen from Prosensa Holding N.V.

Chris Tobias

Both are personalized therapies that target "exon-skipping," a process thought to amend genetic mutations that interfere with dystrophin expression in those with the disease. Both work on a specific exon (exon 51), which cause about 12.5% of the 30,000 cases worldwide. Drisapersen even scored FDA's Breakthrough Therapy Designation. Christopher Tobias, PhD, EVP and chief scientific officer at ad agency Dudnyk, says he's been impressed with the molecules' ability to "go where they need to" and prevent the gene mutation from stopping transition of the dystrophin protein.

But both drugs have had setbacks. In September, GlaxoSmithKline and Prosensa, which had been co-developing drisapersen since 2009, announced that it failed to meet the primary endpoint (statistical improvement in a walking test) in a double-blind, placebo controlled Phase-III trial.

The failure of the competitor product caused the FDA pause. Two months later, Sarepta was told it should not seek accelerated approval for eteplirsen based on Phase-II data alone.

In light of drisapersen's failure, the FDA feared a disconnect, Sarepta said, between "increased expression of dystrophin and clinical efficacy for drisapersen." That, plus negative reports about a previous drug thought to act by increasing dystrophin, "raise 'considerable doubt' about both the dystrophin biomarker and the supportive clinical efficacy assessed on the 6-minute walk test (6MWT) in the Phase IIb clinical study of eteplirsen."

Yet hopes were renewed when, at press time, Sarepta released 120-week results showing its drug demonstrated continued ability in helping boys perform well on the 6MWT, and that patients on the drug were able to walk 64.9 meters farther than the placebo group.

The data could give Sarepta a leverage point with the FDA, says Tobias. "FDA likes (needs) to see validated functional tests," he says. "The problem stems from the fact that as these children age, they are always getting a little bit worse, and there is heterogeneity in their ability to walk at each age. Moreover, many are in a wheelchair…They don't have another good endpoint for people who can't walk."

In January, GSK parted ways with Prosensa around the development of drisapersen. Prosensa says its DMD portfolio includes drisapersen and five other RNA-based compounds.

Sarepta, which was expected to have a new clinical trial protocol in hand by mid-year, feels the 120-week data could give it a boost. The big question for 2014 is whether it can work with the FDA to identify endpoints agreeable to the agency so that it can move eteplirsen, and its other DMD candidates, forward.

However, the very fact that orphan-better drugs are "merely" more convenient and tolerable than the original orphan drugs has renewed questions about their price. Procysbi reportedly costs $250,000 a year on average, Cystagon about $8,000.

Yet, despite some push-back in 2013 over their premium prices from payers, the orphan space has remained relatively open from the standpoint of payer restrictions. Experts attribute this to the small number of patients, as well as the fact that companies have done an effective job educating payers on the value proposition around the devastating, costly nature of these illnesses.

"Orphan companies are doing a good job of setting up the fundamental context for payers, a critical precursor to the value of what insurers are going to pay for," says Mike McLinden, Mc|K chief strategy officer. Which is not to say that pricing pressure won't emerge in the future as costs rise. EvaluatePharma predicts that orphan drugs will account for 15.9% of global Rx sales by 2018, excluding generics, up from 10% in 2012.

Companies in this space are also striving to help patients and caregivers navigate the process of obtaining care. Consider the challenge of speed to diagnosis. At the present time, according to the Rare Disease Impact Report published by Shire in 2013, it can take, on average, more than seven years in the US and five years in the UK for a patient with a rare disease to receive a proper diagnosis.

Respondents said that, in order to get a proper diagnosis, a patient typically visits up to eight physicians—four primary care and four specialists—and receives two to three misdiagnoses.

Primary care physicians have less time not only to learn about rare diseases, but also to render such a diagnosis. Data from the National Institutes of Health (NIH), Office of Rare Disease Research has shown that there are around 500 diseases common enough to be in any physician's repertoire for diagnosis, while another 6,500 are known but are very rare, notes Wendy White, founder and president of the rare-disease relationship marketing agency Siren Interactive.

Siren is seeking to leverage technology to speed diagnosis. It's collaborating with MIT, Global Genes and local biopharma companies on a rare disease "hackathon" to develop a tool to help physicians recognize diseases they may never see in their practice. "The idea of hackathons—bringing cross-functional teams together to solve big problems—will really help move things forward," explains White.

Fellow orphan and specialty marketing shop Cambridge BioMarketing is seeking to crack the diagnosis code another way. "If you can work with large [hospital] networks and devise ways to comb through patient data…you could cut the time to diagnosis dramatically," says Cambridge's Hodgson.

One client has asked the agency to develop a "worm" that can crawl though health systems' electronic medical records to identify subtle patterns suggestive of certain rare diseases. It's partnering with EMR outfit Epic on the initiative.

Compass Healthcare's Nalen says he believes that better diagnosis will continue to be a function of empowered, passionate individuals acting as their own healthcare advocates. He foresees technology being harnessed in the orphan space for self-diagnosis via mobile apps.

"More and more people are going to self-diagnose, aided by digital tools," especially in light of the shortage of PCPs, Nalen predicts.

That could go a long way toward alleviating the significant challenge of obtaining an accurate diagnosis, a barrier which persists, even amid the healthy crop of orphan NMEs: Nalen says he anticipates 14 orphan-drug launches this year. ■