Rare Diseases

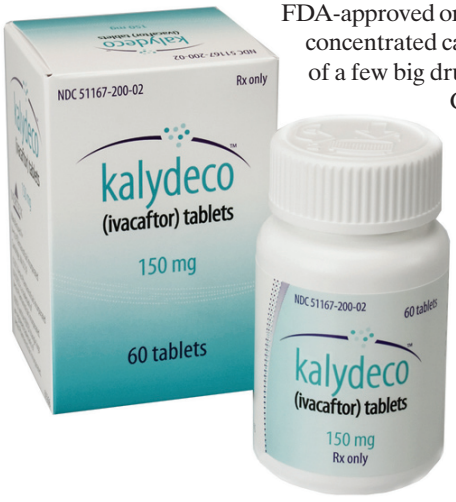
Companies are looking carefully at the rare disease area now, especially given last year's robust wave of approvals. But there's a steep curve. Beyond small patient populations, firms in this burgeoning space face a host of unique challenges. **Noah Pines** reports

As the Orphan Drug Act (ODA) turns 30 this year, those who had a hand in facilitating its passage would be taking heart now that innovative medicines for rare diseases are roaring into the spotlight. Of the 39 products that the FDA approved in 2012, about a third carried orphan status. That includes NMEs as well as existing, re-tasked products.

"The market is hot—it is a space companies are looking at very carefully right now," says Peter Saltonstall, who heads the National Organization for Rare Disorders (NORD).

Few of these will achieve the commercial stardom of juggernauts like Alexion hematology drug Soliris or Novartis cancer med Gleevec. Among the first orphan blockbusters, these drugs showed that premium pricing and the ability to push into multiple indications could offset the typically small patient population (per the ODA, less than 200,000 in the US).

As these drugs increasingly show up on payers' radar screens, the view on coverage is likely to evolve, and newer orphan brands have a steep path to profitability. It's no surprise, then, that the list of companies in the field is a fairly compact one, as can be seen on the table at right, which culls from the 400 or so FDA-approved orphan drugs to show the most concentrated categories. With the exception of a few big drugmakers like Sanofi, whose Genzyme products collectively account for less than €2 billion in sales, those active in the space tend to be small-to-medium size biotechs.



And despite lip service to the contrary, we're not likely to see more big pharmas look to orphan drugs as an antidote to the patent cliff, says the Bernstein Research analyst Tim Anderson, MD. The rare disease model is one "that they [big pharma] don't have long experience with," Anderson says. "It is about hands-on, long-term, deep approaches. It is not like pharma can just pick it up. It is out of their wheelhouse."

Indeed, sources say, companies large and small in this burgeoning therapeutic space are re-writing the traditional promotional playbook that pharma has relied on for decades.

"You can't assume that drivers of success in the pharmaceutical industry will be the same for rare disease products," explains Sylvie Grégorie, PharmD, president of Shire Human Genetic Therapies. This new set of rules extends across the continuum, from early clinical development (see "Clinical Corner," p. 42), marketing planning and customer engagement to the very role of the company sales rep.

Mike Scott, EVP with Independence HealthCom Strategies Group and the current chairman of NORD, notes, "It is not a matter of mass marketing; it is a highly targeted form of communication," in terms of identifying patients and the doctors who treat them, and working very closely with the rare disease advocacy organizations, who know this, to be able to get the right information to the right people.

For instance, Kalydeco (ivacaftor, or VX-770) won FDA approval last year. Years prior to launching the cystic fibrosis drug, Vertex Pharmaceuticals nurtured a close partnership with the Cystic Fibrosis Foundation. Besides helping Vertex identify patients for trials, the foundation assisted with an extensive campaign to educate the community about the need for genotype testing, which determines their eligibility for the product.

"There is a rather significant education portion to the community about why genotype matters," notes Megan Goulart, Vertex senior manager of CF product communications & patient advocacy. "It's a whole new way of thinking about disease and treatment, because until now, a patient's genetic mutation, or genotype, did not impact what treatment their doctor prescribed. And now it does."

In this case, education about diagnosis is more important than product promotion. The underlying strategy being that patients

TOP RARE DISEASE PRODUCT AREAS, 2012

Most concentrated orphan drug categories, by their number of FDA-approved products†, plus products' sales (global) and media spend (US)

Product	Manufacturer	Global sales dollars (millions)*	% change vs. prior 12 mos.	US total media spend dollars (thousands)**	% change vs. prior 12 mos.	US DTC media spend dollars (thousands)	US journal spend dollars (thousands)
HEMOPHILIA							
AlphaNine	Grifols Biologicals	N/A	N/A	$0.0	N/A	$0.0	$0.0
BeneFix	Pfizer	$693.0	7.8%	$92.3	1,141.1%	$0.0	$92.3
Desmopressin acetate	Generic	N/A	N/A	$0.0	N/A	$0.0	$0.0
Humate-P	CSL Behring	N/A	N/A	$0.0	-100.0%	$0.0	$0.0
Kogenate	Bayer HealthCare	$1,075.0	7.1%	$84.1	N/A	$0.0	$84.1
Mononine	CSL Behring	N/A	N/A	$0.0	N/A	$0.0	$0.0
Novoseven	Novo Nordisk	N/A	N/A	$174.2	80.9%	$0.0	$174.2
Refacto	Pfizer	$506.0	25.0%	$0.0	N/A	$0.0	$0.0
CHRONIC MYELOGENOUS LEUKEMIA							
Bosulif	Pfizer	N/A	N/A	$54.5	N/A	$0.0	$54.5
Gleevec	Novartis	$4,659.0	9.2%	$323.5	-51.8%	$0.0	$323.5
Roferon A	Roche	N/A	N/A	$0.0	N/A	$0.0	$0.0
Sprycel	Bristol-Myers Squibb	$803.0	39.4%	$625.3	-43.7%	$0.0	$625.3
Synribo	IVAX	N/A	N/A	$0.0	N/A	$0.0	$0.0
Tasigna	Novartis	$716.0	79.5%	$1,298.3	-25.1%	$0.0	$1,298.3
CHRONIC LYMPHOCYTIC LEUKEMIA							
Arzerra	GlaxoSmithKline	N/A	N/A	$933.0	6.2%	$0.0	$933.0
Campath	Genzyme	N/A	N/A	$0.0	N/A	$0.0	$0.0
Fludara	Genzyme	N/A	N/A	$0.0	N/A	$0.0	$0.0
Fludarabine phosphate	Generic	N/A	N/A	$0.0	N/A	$0.0	$0.0
Rituxan	Genentech/Roche	$6,005.0	8.0%	$0.0	-100.0%	$0.0	$0.0
Treanda	Cephalon/Teva	N/A	N/A	$1,371.4	3.0%	$0.0	$1,371.4
PULMONARY ARTERIAL HYPERTENSION							
Adcirca	Eli Lilly	N/A	N/A	$0.0	-100.0%	$0.0	$0.0
Letairis	Gilead	N/A	N/A	$97.4	-27.5%	$0.0	$97.4
Remodulin	United Therapeutics	N/A	N/A	$0.0	N/A	$0.0	$0.0
Tracleer	Actelion	$1,630.2	-7.0%	$54.9	-89.7%	$0.0	$54.9
Tyvaso	United Therapeutics	N/A	N/A	$164.1	134.2%	$0.0	$164.1
Ventavis	Actelion	$114.0	-10.4%	$70.7	-76.8%	$0.0	$70.7
LENNOX-GASTAUT SYNDROME							
Banzel	Eisai	N/A	N/A	$188.4	157.4%	$0.0	$188.4
Felbatol	Meda Pharma	N/A	N/A	$0.0	N/A	$0.0	$0.0
Lamictal	GlaxoSmithKline	N/A	N/A	$943.0	30.2%	$0.0	$943.0
Onfi	Lundbeck	N/A	N/A	$496.5	N/A	$0.0	$496.5
Topamax	Johnson & Johnson	N/A	N/A	$0.0	N/A	$0.0	$0.0
MULTIPLE SCLEROSIS							
Ampyra	Accorda Therapeutics	$210.5	N/A	$978.4	40.2%	$0.0	$978.4
Avonex	Biogen Idec	$2,700.0	7.0%	$1,090.2	-43.2%	$0.0	$1,090.2
Betaseron	Bayer HealthCare	$1,196.3	-7.4%	$58.8	-68.8%	$0.0	$58.8
Copaxone	Teva	N/A	N/A	$514.3	75.5%	$0.0	$514.3
ANGIOEDEMA/HAE							
Berinert P	CSL Behring	N/A	N/A	$0.0	N/A	$0.0	$0.0
Cinryze	ViroPharma	N/A	N/A	$106.1	-44.6%	$0.0	$106.1
Firazyr	Shire	$33.0	197.3%	$0.0	N/A	$0.0	$0.0
Kalbitor	Dyax	N/A	N/A	$72.5	-38.2%	$0.0	$72.5
CYSTIC FIBROSIS							
Cayston	Gilead	$77.5	84.0%	$0.0	N/A	$0.0	$0.0
Kalydeco	Vertex	N/A	N/A	$144.8	N/A	$0.0	$144.8
Pulmozyme	Genentech/Roche	N/A	N/A	$0.0	N/A	$0.0	$0.0
Tobi	Novartis	$296.0	6.1%	$0.0	N/A	$0.0	$0.0
MUCOPOLYSACCARIDOSIS							
Aldurazyme	BioMarin/Genzyme	$82.8	16.3%	$20.6	35.0%	$0.0	$20.6
Elaprase	Shire	$464.9	15.0%	$0.0	N/A	$0.0	$0.0
Naglazyme	BioMarin	$224.9	16.7%	$0.0	N/A	$0.0	$0.0

*Global 2011 sales, where available **DTC/journal spend between Dec. 2011 and Nov. 2012 inclusive. Sources: FDA Orphan Drug Product designation database; sales, the companies; DTC media spend, Nielsen; journals, Kantar Media. † Includes products with orphan drug designation. Not a comprehensive list.

CLINICAL CORNER

Aside from the commercial implications of pharma's interest in small disease populations, the trend has multiple effects on development.

The upside: some very nice tax benefits for manufacturers, which Chris Tobias, MD, EVP and chief medical officer at Dudnyk, rattles off as: "Fifty percent of R&D efforts come back as tax credits; you have seven years of exclusivity; and FDA waives the fees for the drug approval application. Orphan drugs also can get approved in a shorter time frame."

Sylvie Grégorie

On the other hand, manufacturers face a host of technical challenges, says Shire Human Genetic Therapies president Sylvie Grégorie, PharmD. "With many rare diseases, there are often no natural history studies, which means that the company needs to undertake its own original research to identify endpoints to pursue or where to intervene in the course of disease.

"Once an endpoint has been determined, there is also the challenge of finding patients who are at the same point in their illness, which creates a hurdle in terms of recruiting enough centers," Grégorie continues. "There are also questions of how long is it going to take before one can demonstrate a benefit, whether a control arm is needed, whether it is even ethical to have a placebo arm and/or whether the parents give consent."

With such small numbers, "Everyone is trying to find solutions for getting a robust patient base," adds Alex Kondo, senior offerings manager, clinical trial optimization solutions at IMS Health.

Recruiting for randomized trials is hugely difficult. "Let's say there are 5,000-6,000 patients in the US," says Tobias. "To find them and get them enrolled in a clinical study is hard." Even if you do, it may be more difficult to demonstrate a statistically meaningful effect.

One example is mantle cell lymphoma (which constitutes 5% of all non-Hodgkin's lymphoma). "There are numerous options for initial therapy and at relapse, so comparison studies are difficult given the different possible 'control' group options," says John Leonard, MD, who heads the new clinical trials office at Weill Cornell Medical College and specializes in clinical trials in oncology.

The scope of customers is limited even further when multiple companies are developing a product for a single indication. Here's where patient advocates can help. Commenting on how patient groups set up clinical trial networks and patient registries, Frank Sasinowski, a lawyer who helped draft the 1983 Orphan Drug Act, says, "What you're seeing is a window on the future of drug development—people who know a disease, who are committed to it, who get the funds and who organize the trials themselves."

Given this emerging dynamic, Dr. Tim Cote, a consultant who used to head FDA's Office of Orphan Drugs, says, "You can develop a drug for less than $200 million. You can get a drug approved with 50 patients." *—Noah Pines and Marc Iskowitz*

with rare diseases are often hard to diagnose, and once diagnosed they will consistently take an approved drug.

In contrast to marketing large brands, companies must connect with small communities of patients and caregivers, often online, and focus on user experience. "You've got to look at the patient flow and how a lot of the patients come to be diagnosed," says Lynne Powell, VP of commercial operations at CSL Behring, whose orphan portfolio includes such brands as Berinert, for herediatry angioedema (HAE). "Many of them may go many years before they are diagnosed." The drugmaker helps in securing reimbursement, as well as offering peer-to-peer support that connects patients with others suffering from the disease.

Furthermore, when it comes to physician education, most practicing doctors hardly ever see a patient with a truly rare disease, says Siren Interactive founder and president Wendy White, so unless they're one of the world's five experts, they don't have the time or the bandwidth to learn about it until there is a patient right in front of them. "The education needs to be 'just in time.'"

Fewer involved physicians means there's less need for an army of sales reps to "fill the funnel" in terms of getting more doctors to write 'scripts. "Given that 80% of rare diseases affect children, it is the parent who is the lead healthcare expert of the house," explains Peter Nalen, president and CEO, Compass Healthcare Marketers. "Often the patients and families are educating the doctor about the condition," adds Mike Hodgson, chief creative officer, Cambridge BioMarketing. Reps therefore take on a much broader role in educating the various stakeholders and working with the patients and the caregivers to help with reimbursement, fulfillment and adherence.

As additional orphan medications emerge, biotechs are understandably worried about reimbursement resistance. But experts say they are less concerned about there being dramatic pushback on coverage for rare-disease medications in the near-term, simply because there are so few patients and because spiraling costs (which can exceed $400,000 per patient per year for some therapies), and the corresponding demand among payers for value has led to development of products that have a dramatic impact on patients' lives.

Shire's Grégorie tells *MM&M*, "When you take all of this into consideration, the reality is that it is not an egregious cost to the system. In fact, it forces us to focus our efforts on therapies that will be significant to the patient and will be paid for by the payers."

Still, manufacturers need to do their homework. The pharmacy and medical P&T directors will ask, "'What are you doing to ensure that a patient going on therapy is going to succeed? What are you doing to ensure that caregivers are involved and fully on-board?'" says Havas Health's Khawar Khokhar, head of market access and business-to-business marketing.

They must also demonstrate how use of the product is somehow more cost effective than no treatment or other modalities. Ruth Suter, senior director, market access and patient services at BioMarin Pharmaceuticals, says the biotech is "exploring models to illustrate the potential budget impact for therapies without meaningful competition, as well as publishing information to support this economic modeling." Adds Dennis Jackman, SVP, public affairs at CSL Behring, "Sometimes [therapies] may fall outside of the traditional health outcomes measurements. Other considerations should be taken into account, like societal benefit, seriousness of the condition, and the small populations for statistical studies." ■