Orphan Drug Marketing

Data and expert insight for physician, patient and payer outreach

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Market Overview
Small Wonder

Once largely ignored by biopharma, orphan-disease products have come roaring into the spotlight. The trend underscores how the patent cliff on mass-market brands, and the quest for personalized medicine, are driving industry down a new path. **Noah Pines** reports

Although the Orphan Drug Act (ODA) turns 30 this year, it's only been in the last decade or so that the market has really taken off. Last year orphan meds accounted for 10% of worldwide prescription sales, up from 6% in 2003. Sales rose 7.1% to $83 billion in 2012 and are set to grow by 7.4% per year between 2012 and 2018 to $127 billion, according to EvaluatePharma.

Since the Act was promulgated in 1983, FDA's Office of Orphan Products Development (OOPD) has seen the development and marketing of over 400 drugs and biologic products for rare diseases, those that affect less than 200,000 people in the US. The agency says about a third of new drugs approved each year meet that definition. And indications are that interest is growing: Requests for orphan drug designation reached 264 in 2012, although the number has fallen the past two years.

"From start-ups to pharma bellwethers, industry is focusing on rare diseases

Among those recently green-lighted by the agency, two were for homozygous familial hypercholesterolemia (HoFH), an ultra-rare inherited cholesterol disorder affecting about 3,000 patients in the US. The approvals came just a month apart—Sanofi's Kynamro in January 2013, preceded by Aegerion's Juxtapid in December.

They underscore how firms, from small start-ups founded in suburban kitchens to big pharma bellwethers, are recognizing how potentially lucrative it is to focus on rare diseases. Small patient numbers are often offset by premium prices. Juxtapid, for instance, costs upwards of $295,000 per patient per year; Kynamro $176,000 per patient per year.

Having churned out remedies for many of the chronic Western ailments—and in many cases having watched these mega-brands in crowded categories topple to generic oblivion the past two years—industry is replacing them with treatments for tiny populations.

Since many of the larger medical conditions will be treated with generics over the next 15-20 years, it is the smaller conditions that offer industry the greatest opportunity to innovate.

Medical science is starting to sub-classify major illnesses into smaller disease entities. Pfizer's Xalkori was approved and found a niche in the 4% subset of NSCL cancer patients who are positive for the ALK-fusion gene, an example of personalized medicine.

Smaller patient pools have advantages for companies, who get to leap onto the express lane of clinical development and approval. "In rare diseases, yes, you can develop a drug for less than $200 million, and yes, you can get a drug approved with a study involving 50 patients," says Tim Coté, a physician and industry

"Finding cures to individual rare diseases opens doors to treating more common disorders"

—Mike Scott, *chairman, National Organization for Rare Disorders*

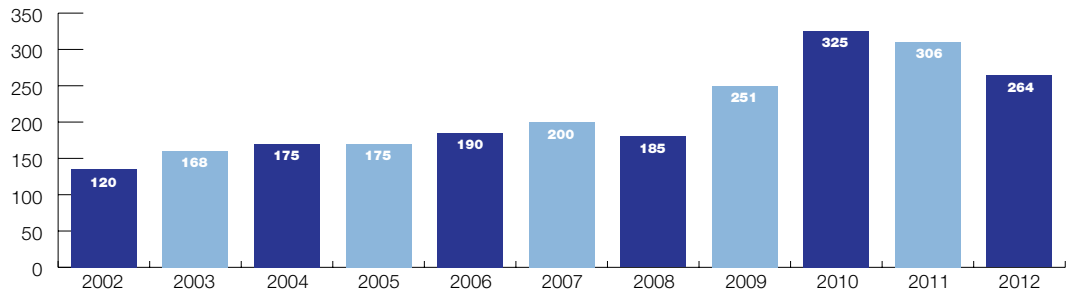
15.9%

of global Rx sales will come from orphan drugs by 2018, excluding generics, up from 10% in 2012

(Source: EvaluatePharma, Orphan Drug Report 2013)

Trending up

Manufacturer requests to the FDA for orphan-drug designation



Source: FDA

Market Overview
Small Wonder

Top 10 companies by orphan drug sales, 2012

Rank	Company	W/W orphan sales ($ billions)
1	Novartis	$10.9
2	Roche	$9.0
3	Pfizer	$5.4
4	Celgene	$4.9
5	Bayer	$4.2
6	Sanofi	$2.9
7	Baxter International	$2.5
8	Bristol-Myers Squibb	$1.7
9	GlaxoSmithKline	$1.4
10	Alexion	$1.1

Source: EvaluatePharma, Orphan Drug Report 2013

consultant who was previously director of OOPD.

The ODA also promises longer patent protection (seven years vs. five), plus other advantages that have spurred manufacturers on the R&D front.

"Finding cures to individual rare diseases opens doors to treating much more common disorders," points out Mike Scott, current chairman of the National Organization for Rare Disorders (NORD). That helps bring in revenue to fund further R&D.

A well-known example is Novartis' oncology pill Gleevec (Glivec outside of the US). Initially approved for a rare form of leukemia, Gleevec today has 11 indications and took in $1.7 billion in US revenue last year, according to IMS Health.

As they gear up for launch, manufacturers "can't assume that the drivers of [commercial] success…will be the same," says Sylvie Grégoire, PharmD, former president of Shire's orphan drug unit, Shire Human Genetic Therapies. The new playbook extends from early clinical development, marketing planning and customer engagement to the role of the sales rep.

For one, "Given that 80% of rare diseases affect children, it is the parent who is the lead healthcare expert of the house," explains Peter Nalen, CEO of Compass Healthcare Marketers.

By leveraging patient groups, caregivers and advocacy organizations, as well as a small cadre of key opinion leaders (KOLs), commercialization costs can be dramatically lower than budgets for major pharma brands.

Going forward, the biggest challenge rare-disease marketers will face is one of how to price offerings. The fact that these treatments usually are "life-enhancing" for a few patients means "there have not been a lot of issues with getting reimbursed," says Mike Hodgson, EVP of Cambridge BioMarketing.

However, payers and providers are starting to question high prices. The conversation of what to charge, how to recoup the value for orphan products, and how to foster a sustainable model of pricing will be a critical ongoing conversation.

All of this adds up to the continued need for manufacturers to demonstrate the value of their products, particularly vs. current modalities.

"If, as a payer, it is already costing me a million dollars a year in hospital- and emergency-care costs to treat a rare disease, then it may be perfectly reasonable to charge a premium for a drug that keeps patients out of the hospital," notes Scott, who is also an EVP with Independence HealthCom Strategies Group. "But we need to do those economics." ■

Top 10 orphan drugs by sales, 2012

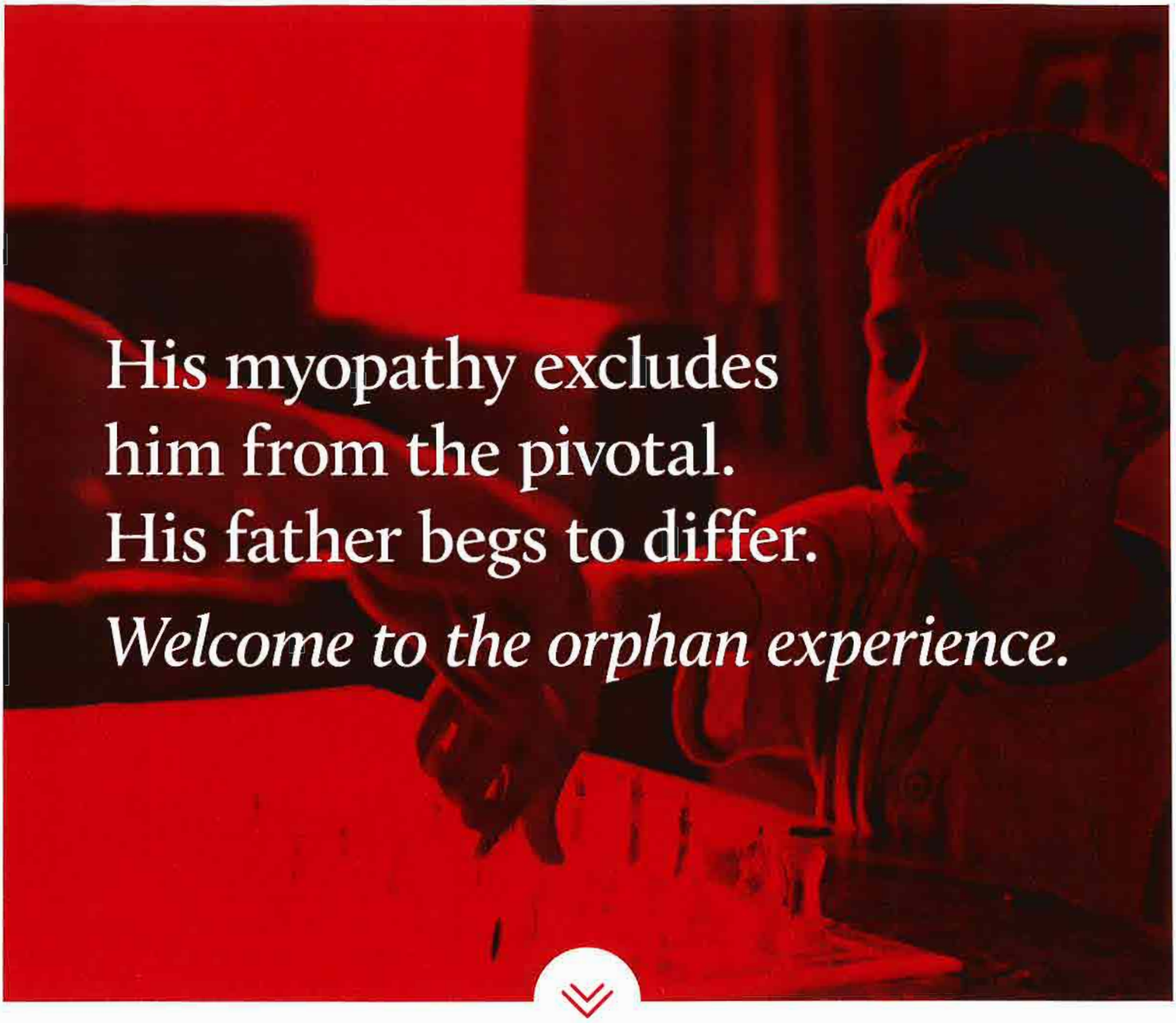
Rank	Product	Company	W/W orphan sales ($ millions)
1	Rituxan	Roche	$7,155.0
2	Revlimid	Celgene	$3,767.0
3	Avonex	Biogen idec	$2,913.0
4	Alimta	Eli Lilly	$2,594.0
5	Velcade	J&J/Takeda	$2,358.0
6	Soliris	Alexion	$1,134.0
7	Sprycel	BMS	$1,019.0
8	Tasigna	Novartis	$998.0
9	Afinitor	Novartis	$797.0
10	Yervoy	BMS	$706.0

Source: EvaluatePharma, Orphan Drug Report 2013

"You can develop a drug for under $200M. You can get a drug approved with a study of 50 patients"

—Tim Coté, *MD, MPH, former director, FDA Office of Orphan Products Development*

13 The number of new molecular entities (NMEs) the FDA approved in 2012 for rare diseases, up from 11 in 2011



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Physician Marketing
Zebra Spotting

Most physicians are trained to think of the most common diagnosis first, but what clinician isn't intrigued by the thought of diagnosing a rare case? Here are some pointers on tailoring messages to providers about one-in-a-million diseases

The term "zebra" is doctor-speak for a rare diagnosis. It's become part of the well-known medical aphorism, "When you hear hoofbeats, think horses, not zebras."

Yet "when they hear hoofbeats coming along, physicians need to think it could be a zebra," says Mike Hodgson, EVP and chief creative officer of Cambridge BioMarketing. "There aren't a whole lot of zebras in their backyard. But when they see one, it's extraordinary and unexpected—and there is a thrill of then offering something to that patient which is powerful and lifesaving."

So the key, says Hodgson, is to tell the unique story behind disease and therapy. Since most orphan diseases are treated by specialists, companies can do this through smaller, more highly-trained sales forces whose role is mostly to facilitate disease identification, while combating misdiagnosis and under-diagnosis.

> **"There is a thrill of offering something which is powerful and lifesaving**

"A physician may see a rare disease patient every one-to-two years," adds Chris Tobias, PhD, an EVP at Dudnyk. "Therefore, communication needs to be crystal clear, and educational training modules need to help [clinicians] remember it…The good news is that in orphan diseases, you get 15-20 minutes."

Clinical educators from Vertex Pharmaceuticals, for instance, collaborate with various members of the cystic fibrosis care team within a treatment center—the nurse, respiratory therapist and social workers, in addition to the pulmonologist—about new CF treatment Kalydeco, helping them understand the product and offering reimbursement support.

However, since they see so few patients with an obscure illness, physicians may not "have the time [or] the bandwidth" to stay abreast of the intricacies, says Wendy White, who founded the agency Siren Interactive. Unless the doctor is one of the world's five experts, she says, "The education needs to be 'just in time.'"

This factor, along with budget constraints, has prompted many companies to turn to non-personal communication. They are leveraging search engines, for example, by optimizing the symptoms a physician might be looking for information on, then driving HCPs to biopharma websites.

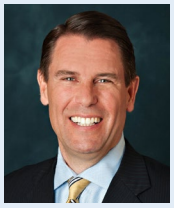
The Manhattan Research-Google Physician Channel Adoption Study (June 2012) showed 84% of physicians use search engines daily for practice information, and 32% click on paid search first.

Moreover, 44% of doctors watch YouTube for professional purposes, and many of them are accessing rare-disease information, says White. With so many physicians, patients and caregivers going online for rare-disease information, companies also offer on-demand webinars and videos.

In the case of CSL Behring, whose orphan portfolio includes such brands as Berinert for hereditary angioedema (HAE), "We provide CME training…to help physicians diagnose these diseases and treat effectively," notes Lynne Powell, VP of commercial operations.

Speaker programs and medical conferences can also get the word out. Alexion Pharmaceuticals used these tactics to enhance diagnostic programs when Soliris won a second orphan indication, atypical hemolytic uremic syndrome (aHUS). ■

Telling the rare-disease story to docs



Since the number of specialists likely to see a patient with a rare disease is relatively small, the story of an orphan disease and therapy can be told with a smaller sales force. And reps are likely to get more face time with a doctor, on the order of 15-20 minutes vs. the typical 2-3 minutes allotted for a mass-market drug detail.

Biotech firm Aegerion is using 25 reps to target academic lipid specialists, community-based specialty lipidologists and cardiologists during the US launch of Juxtapid, a once-daily pill green-lighted by the FDA last December for homozygous familial hypercholesterolemia (HoFH), an ultra-rare cholesterol disorder affecting about 3,000 people in the US.

In the first quarter, SG&A costs were $13.2 million. "We have over 45 speaker programs scheduled in Q2 and Q3 in the US for cardiologists," said CEO Marc Beer (pictured). In June EU advisors issued a positive opinion. Aegerion hasn't publicly stated the number of reps it will launch lopitamide with in Europe.

> **"There aren't a whole lot of 'zebras' in their backyard. But when they see one, it's extraordinary"**
>
> —Mike Hodgson, *EVP/chief creative officer, Cambridge BioMarketing*

25 sales reps are targeting specialists for US launch of Aegerion's new rare-disease therapy Juxtapid

She is an influencer, a decision maker, and an advocate for your brand

Patients with rare diseases are powerful decision makers. After years of misdiagnosis and misinformation, they have learned how to champion their own health needs. They aggressively seek information, stay up to date on the latest clinical advances, and actively share their knowledge and opinions with others in the patient community. They know more about their medical needs than most healthcare providers, and they will relentlessly advocate for treatments that can help.

As the leading agency exclusively focused on patients with rare diseases, Compass Healthcare Marketers has expert capabilities in developing deep connections with patients in the rare disease community and proven strategies to help marketers of orphan drugs establish authentic, enduring relationships that lead to healthy outcomes for patients and your brands.

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Patient Communities
A Close Encounter

Experience dictates putting the caregiver, patient and tight-knit community at the center of any rare-disease marketing plan. More than anything, success hinges on marketers' ability to build trust through credibility and value

Pharmaceutical companies typically market brands for large, chronic illnesses to consumers through mass DTC advertising. But marketing a rare-disease drug involves building authentic, one-to-one relationships with micro-communities.

Drug makers that have honed the process say the best way is to ally with patient advocacy groups during the R&D phase. Vertex Pharmaceuticals did so when connecting with patients and caregivers in the small cystic fibrosis (CF) community.

"We worked with the CF Foundation to help change the thinking about disease," says Megan Goulart, Vertex senior manager of patient advocacy.

The foundation helped not only find patients and to understand what they're going through but also, prior to the launch of CF drug Kalydeco in 2012, spread the word about the need for genotypic testing.

> **"Tapping into patient communities starts with a one-to-one relationship**

Patient groups typically start as homespun efforts—a concerned mother looking for information about her child's disease, for instance. They are receptive to information from companies. However, patients often trust other patients most.

Lynne Powell, CSL Behring VP of commercial operations, says one of the company's "most successful programs" is its Voice2Voice initiative, in which the rare-disease drug maker enlists patients taking its drug Hizentra or their caregivers to connect with those newly diagnosed with primary immunodeficiency, or PI.

These "advocates" do everything from share their stories to answer non-medical queries. (Hizentra, which does not have orphan drug designation, was approved by the FDA for PI in 2010.)

Marketing experts also recognize the vital importance of online patient communities and social networking sites to forging bonds. It's the virtual water cooler where the rare-disease community clusters, the native soil where they germinate and grow.

Social media is where micro-communities grow. Above: Facebook page for the Huntington's disease community, sponsored by Lundbeck

"Often the patients and families are educating the doctor about the condition," says Mike Hodgson, EVP, Cambridge BioMarketing. But it's a double-edged sword. "If they have a bad experience with you, people are going to tweet about it," says Hodgson.

News and information—good or bad—travels quickly. "Manufacturers need to build a very honest, direct relationship with people in the community because it is a direct reflection of the company and the brand," says Peter Nalen, CEO of Compass Healthcare Marketers.

Agencies can tell you what the social-media "chatter" is. Alex Zukiwski, chief medical officer of biotech Arno Therapeutics, suggests, "Sit at the table with the patients and their family. Once you start to understand what their life is like, your job becomes much easier and a lot more fulfilling."

Companies should also determine how best to enhance the user's experience. And that extends beyond the medication itself, to adherence support, reimbursement assistance, or programs to ensure access should the patient lose insurance. These should all be accessible seamlessly, says Nalen, via one phone number.

Above all, expect closer connections. These patients require more services from a manufacturer. And since most rare diseases are chronic and begin in childhood, the relationships can last a lifetime. ■

> **"Sit down with patients and see what their life is like. Your job becomes easier, more fulfilling"**
>
> —Alex Zukiwski, *chief medical officer, Arno Therapeutics*

67% of US patients and caregivers need to educate their doctors on their rare disease

(Source: Rare Disease Impact Report, Shire, 2013)

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Reimbursement
The Payer Struggle

Given their efficacy against life-threatening diseases, orphan drugs can command huge prices. There's been no real push-back from payers—yet—but MCOs need more information to make decisions, and this is an area where drug makers can help

Rare diseases have become one of the pharmaceutical market's most prolific and profitable sectors, climbing 7.1% in 2012 to approximately $83 billion worldwide, according to a report from EvaluatePharma. And the market for orphan treatments is forecast to grow to $127 billion by 2018.

That's in large part due to the multiple six-figure prices companies can charge. The underpinning for most firms' reimbursement strategy is that the market for the drugs is tiny and that they often are highly effective in the small populations for which they are indicated, mostly children.

"Health plans are required to cover orphan drugs and cannot deny access," says Rhonda Greenapple, founder and CEO of Reimbursement Intelligence. The products do undergo review by a plan's Pharmacy & Therapeutics Committee, but not the six- to 12-week review typical for traditional drugs. They're covered immediately, she says.

> **Payers are likely to develop more rigorous criteria**

Also, since there is no true comparator product in many cases, all an orphan drug needs to show is some improvement over current treatments or no treatment.

Experts don't expect sudden changes for access in the US. Some say rare-disease meds dodged a bullet when their funding was not undercut by the new health law.

As costs rise, some wonder if full access can continue. Alexion's drug Soliris—the only med approved to treat two ultra-rare, life-threatening blood diseases—is the world's most expensive medication at about $440,000 per patient per year. Alexion and other orphan-drug makers have met resistance from government payers overseas (see sidebar). Against the backdrop of an evolving US healthcare system, one can envision a tipping point where there is payer recalcitrance or where co-payments for new medications exceed patients' ability to pay.

Experts say biopharma senior management teams should not assume that rare-diseases prices are infinitely elastic in this country. "A model in which we sub-divide all disease down to tiny sub-sets of patients, and where the price is $400,000 is not sustainable," says Mike Scott, chairman, National Organization for Rare Disorders.

In such circumstances, look for MCOs to develop more rigorous criteria. Questcor Pharmaceuticals raised hackles, but only after aggressively marketing its 60-year-old hormone drug H.P. Acthar Gel—priced at $28,000 a vial—for conditions beyond its orphan indication. One insurer said it will stop covering the non-orphan uses.

For now, the only real management option for payers, says Greenapple, is to prior-authorize the product or to assign a very large co-payment or co-insurance, a flat percentage the patient pays. Approximately 25% of health plans have moved to co-insurance, she says. Most manufacturers have assistance programs, in which they promise to reimburse patients for any gap in insurance.

Still, 90% of payers say they struggle with determining how rare diseases should be covered, due to the lack of standards and guidelines. So it remains incumbent on manufacturers to maintain an open dialogue with and educate payers. Those that have been successful in securing coverage have helped MCOs and EU government ministers envision what it costs to treat a given condition absent the medication.

"There is a big disease education component, because payers may have never focused on the category," says Khawar Khokhar, head of market access at Havas Health, "but due to high individual patient costs with small total budget impact, we need to ensure that ultimately the right decisions are made for patients." ■

Europe creates hurdles for orphan drugs

US managed care organizations generally have not balked at the high price tag for treating rare diseases, but European health ministers are proving to be less permissive.

"Reimbursement agencies in the EU are pushing back on the cost of orphan drugs," points out Alex Zukiwski, MD, chief medical officer at Arno Therapeutics.

In January, UK Health Minister Lord Howe (pictured) threw out an advisory panel's positive recommendation for Alexion's Soliris to treat atypical hemolytic uremic syndrome (aHUS), referring review to the National Institute for Health and Clinical Excellence (NICE). The rejection was a first for an orphan drug in the UK. Alexion was reported as saying it was "gravely disappointed" by the decision.

Some say the move signals the start of a tough new stance to funding orphan drugs in the UK market.

"There is a big disease-education component. Payers may have never focused on this category"

—Khawar Khokhar, *head of market access, Havas Health*

90% of US payers say it is more difficult to decide what coverage to provide for patients with rare diseases

(Source: Rare Disease Impact Report, Shire, 2013)

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Regulation
A Fertile Pathway

Lawmakers and regulators on both sides of the Atlantic have tilled the soil for this field to grow rapidly. Still, there are both pitfalls and pluses along the orphan-drug approval pathway

As in any area of drug development, there are unique challenges and opportunities involved in getting orphan medicines approved. The good news: regulatory bodies are more knowledgeable and better-equipped than ever to review these drugs.

It shows in the steady crop of FDA orphan-product designations—2,700 at last count—and approvals, which for years now has held constant at roughly one-third of the overall tally of NMEs green-lighted by the FDA. Last year the agency approved 13.

Things used to be different. Before the Orphan Drug Act (ODA) became law in 1983, few orphan drugs got to market. "The law plus the establishment of NORD [the National Organization for Rare Disorders], which brought the patient community together, created an environment that fostered the development of new orphan drugs," says Wayne Pines, a former FDA associate commissioner.

Congress created economic incentives: a 50% tax credit on R&D cost, research grants and a user-fee waiver. Firms also get seven years' marketing exclusivity. It's 10 years in the EU, and industry has responded—firms in the EU requested, and got, 147 orphan-drug designations last year, up 44% from 2011.

Just as important, both FDA and its European counterpart have become attuned to the need for flexibility in developing and approving orphan drugs. To wit: the median number of study participants in Phase III orphan-drug trials is one-fourth that of studies involving standard meds, according to EvaluatePharma. In turn, Phase III orphan-drug development costs are half that of non-orphan, potentially a quarter with tax breaks.

Still, finding participants can be hard when the total patient pool is, say, 5,000-6,000. This leads to challenges. In the pre-clinical phase, there can be a lack of quantitative natural history data or relevant and validated animal models. Also, small sample sizes create statistical issues.

Then there is the challenge of identifying clinical endpoints that regulators will agree on, and gaining access to regulators. But efforts are under way to make clinical design easier. NORD has been working with the FDA, for example, on a project to incorporate patient information into the process via registries and other means.

Legislation passed by Congress last year enabled FDA's Center for Drug Evaluation and Research (CDER) to add dedicated rare-disease staff. Janet Woodcock, MD, head of CDER, told *MM&M* by email, "Our rare disease staff is working hard to help patient groups develop the tools such as natural history data and biomarkers that will make drug development feasible and attractive in their disease of interest."

> **"Regulatory is not an issue. FDA is committed to working with industry**

Meanwhile, drug makers can do their part. "Having early input from regulators is key," says Alex Zukiwski, MD, chief medical officer of Arno Therapeutics. Lines of communication are open: a few years ago, CDER created the Office of Rare Diseases. It works to facilitate orphan product development and provides another focal point, at the staff level.

Adds Chris Tobias, PhD, EVP and chief scientific officer, Dudnyk, "It is also important to work with patients to determine efficacy parameters." Developing relationships with patient groups can also improve communication and information-sharing.

While experts agree more progress is needed in harmonizing EU-US approval requirements, boosting access to regulators and allowing greater input from clinical experts in study design discussions, regulatory bodies have moved quickly to revamp the approval process.

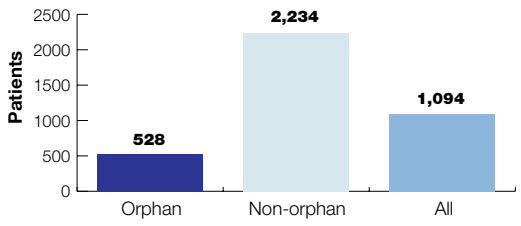
"When all the stakeholders pull in the same direction," says Peter Saltonstall, NORD president and CEO, "I am optimistic that advances will be realized to treat many rare diseases." ■

"Our rare-disease staff is working hard to help patient groups develop tools... that will make [R&D] feasible"

—Janet Woodcock, MD, *director, CDER*

2,700
experimental products have garnered "orphan drug" status from FDA since passage of the Orphan Drug Act in 1983

Sizing it all up
Median Phase III trial sizes for 2012 FDA approvals



Source: EvaluatePharma, Orphan Drug Report 2013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