INNOVATION IS STILL VALUED IN THE ORPHAN-DRUG SPACE, BUT THE REIMBURSEMENT BAR IS RISING. NPS PHARMA'S ERIC PAUWELS, WHO'S LAUNCHED FIVE ULTRA-RARE DISEASE PRODUCTS, EXPLAINS HOW THESE BIOTECH BRANDS CAN DEMONSTRATE THEIR VALUE. ***MARC ISKOWITZ*** REPORTS

ERIC PAUWELS, PRESIDENT, NPS PHARMA INTERNATIONAL

ULTRA MAN

Eric Pauwels has logged five global ultra-orphan drug launches—a track record that makes him a rare find in this most rarefied of biotech categories. But, he's quick to add, he doesn't keep score. "There's nothing homogeneous about launching an ultra-orphan drug," he says. "There's some basics you go forward with, but orphan drugs are all different, like orphan diseases in general."

Pauwels, president of NPS Pharma International, is leading the global market expansion for Gattex/Revestive for short bowel syndrome. His other four launches came with previous employer Shire HGT.

"The ultimate goal is not to be happy with five, we want six," kids the 25-year biotech veteran, referring to the potential approval of what could be the firm's second (and his sixth) orphan-disease product, Natpara for hypoparathyroidism.

Neither Pauwels' in-depth understanding of the sector nor his optimism are likely to fall out of vogue soon. Orphan drugs continue to be a hot category, one where companies can charge premium prices to treat neglected diseases, with little or no competition. Gattex costs $295,000 a year, on par with other ultra-orphan drugs on the market.

The global orphan-drug sector was worth more than $80 billion in 2012, according to an analysis from EvaluatePharma, and about a third of the drugs approved each year by the FDA are for rare diseases, including nine products in 2013.

Drugmakers' familiarity with navigating orphan terrain has come with a risk, though. As treatments fan out to ever more niche indications and subpopulations, one group of stakeholders is becoming more skeptical: payers. It's a new threat to the higher-price-for-a-smaller-patient-population model upon which this category rests.

PHOTO: BILL BERNSTEIN

Demonstrating value

What makes each launch different, and correlates to its ability to secure coverage, comes down to its value proposition. Gattex, which Pauwels successfully debuted in the US last year, was no exception. It's for the 3,000 to 5,000 people nationwide suffering from short bowel syndrome (SBS), those who have lost part of their intestines for a variety of reasons and can't absorb enough nutrients through food, making an intravenous (IV) feeding line necessary for their survival.

The main commercial focus, he says, was on patients, followed by HCPs—a sales force of 24 reps (now up to 36) targeted gastroenterologists—but ensuring managed-markets access was a key goal. "Our product was approved at an annual cost of $295,000, but we had to demonstrate the value proposition to payers," says Pauwels.

During drug development, firms must consider the trials needed to get the product approved from a regulatory perspective and also what surrogate measures are needed to translate the value of the outcome. In the case of Gattex, about two-thirds of trial participants saw at least a 20% decrease in the volume of IV nutrition they required per week. Patients on the drug are believed to be at a higher risk for cancer and other conditions.

MCOs would need to see more than just clinical and safety data. First, "We told them how the burden of illness is extremely high—patients are tethered to an IV line between eight to 10 hours a day, six to seven days a week—and [about] all the complications involved with long-term [IV] nutrition," he says.

Next, NPS introduced the value of the innovation: it's the first and only GLP-2 drug to address the underlying aspects of malabsorption. Then came the hard value-for-money case: that Gattex isn't 100% cost-additive and that it can actually impact directly and indirectly to health system costs.

Standard of care, IV nutrition, "is quite expensive—$100,000 to $200,000 a year, depending on the volume required and the care involved," Pauwels points out. Not to mention that patients with SBS run the risk of infection and other medical complications, and paying for home health aides and hospitalizations can raise the bill. "In many cases, Gattex can reduce that."

The firm also completed studies on the benefits over the long term. As this issue went to press, the FDA had approved updated product labeling to show that patients taking Gattex beyond two years continued to see reductions in their reliance on IV nutrition, including 13 of 88 who were able to completely wean themselves. "That provides [patients] with a significant amount of freedom and independence, which is something you can equate to in terms of value," Pauwels says.

In the US, experts say, there are no federal or MCO requirements for cost-effectiveness data. However, cost-effectiveness evidence is increasingly being submitted and evaluated. That's where "we got a strong reception from payers and… could ensure access," he concludes.

Only one small regional payer has denied coverage. The drug tends to be on a higher tier, but NPS has an access program—NPS Advantage—in place so patients on commercial plans pay no more than $10 out-of-pocket for the drug, and those covered by public payers are directed to a foundation to offset the price.

All of this, combined with other market-development activities, such as patient advocacy and medical education, created a solid foundation for sales. NPS said it penetrated 6% to 10% of the estimated addressable SBS market last year on the way to generating revenue of $32 million. First-quarter 2014 Gattex sales rose 17% vs. the prior year's first quarter, to about $18 million. This year it expects sales to grow to between $100 million and $110 million.

Top 10 companies by orphan drug sales, 2013

Rank	Company	Global sales ($ billions)	% change vs. prior year
1	Novartis	$11.4	4.6%
2	Roche	$9.5	5.6%
3	Celgene	$5.6	14.3%
4	Pfizer	$5.2	-3.7%
5	Teva	$5.1	2.0%
6	Bayer	$4.1	-2.4%
7	Sanofi	$3.2	10.3%
8	Merck KGaA	$3.0	0.0%
9	Biogen Idec	$3.0	3.4%
10	Baxter International	$2.9	16.0%

Source: EvaluatePharma

Top 10 orphan drugs by sales, 2013

Rank	Product	Company	Global sales ($ billions)	% change vs. prior year
1	Rituxan	Roche	$7.5	4.9%
2	Gleevec	Novartis	$4.6	0.4%
3	Copaxone	Teva	$4.3	8.3%
4	Revlimid	Celgene	$4.2	13.7%
5	Avonex	Biogen Idex	$3.0	3.2%
6	Alimta	Eli Lilly	$2.7	4.2%
7	Rebif	Merck KGaA	$2.4	1.8%
8	Advate	Baxter International	$1.9	-5.1%
9	Velcade	Johnson & Johnson	$1.6	10.7%
10	Tracleer	Actelion	$1.6	3.4%

Source: EvaluatePharma

Scrutiny and skepticism

One obvious point about orphan diseases, but one that makes it harder to prove their value proposition, is the fact that they affect a small percentage of the population. "That is the issue at hand," said Monica Martin de Bustamante, managing director of pharma consultancy CB Partners, at the NYBIO meeting in May. "We really don't have that many patients. And…that leads us to various challenges."

For one, it means more incentives are needed for R&D, a higher number of trial sites, and fewer specialists to target. From a pricing and reimbursement perspective, it often means those responsible for making coverage decisions have limited information to go by—either a trial design with no comparator, or a single-arm study with no comparator at all.

"That can lead to difficulties demonstrating cost effectiveness," says de Bustamante, as well as in "the building of a model that has low levels of uncertainty." And in those markets where cost-effectiveness is king (mostly overseas, see sidebar on p. 28), getting access and reimbursement is no slam dunk.

Accelerated approval can exacerbate the situation. "Because we don't have anything available for these patients," says de Bustamante, "we have a desire to get the drug to market faster. From a patient

advocacy perspective, and a desire to launch, there's a bit of a push there. What that tends to lead to is Phase-II trial data as the actual data you're launching with, which means that from a modeling but also from a level-of-evidence perspective, it's much more limited than if you have done full Phase III."

These condensed clinical trial programs mean "you can't develop robust endpoints to support the modeling strategy, or pick the most appropriate [health economics] endpoint or utility metric," explains Sanofi's Meghan Gallagher, who was part of the same NYBIO panel.

"And often in rare diseases, we can't just go and pick off-the-shelf instruments to evaluate our therapies," says Gallagher, director, global evidence & value development/oncology for the drugmaker. "We need to generate our own, because we are the first emerging in this disease state. So we actually need extra time to develop the right sorts of insights we need to support our economic assessments. We're not often blessed with the time to do so."

Orphan drugmakers, Gallagher says, open themselves up to "scrutiny and skepticism" when drawing conclusions about the value of a therapy based on a very small population. "How confidently can you support a value proposition of your therapy if it's based on a very small number of patients scattered across the globe sometimes?"

So the opportunity for manufacturers is also a challenge: being first to bring insights to the market while being vulnerable to payers that can poke holes in your assumptions.

In response to the orphan-drug explosion, US-based insurers are using a variety of management tools. According to data cited by CB Partners, up to 15% of orphan therapies are not covered by Medicare Part D payers. CB Partners has also observed an increase in co-insurance, from 15% to 28%, in the past decade, plus a heavy use of prior authorization. It says that today, at least 11 orphan drugs cost more than $225,000 a year, with others in the $100,000-$225,000 range.

"If you have drugs that are priced at $225,000, $300,000 a year—you probably want to make sure that is an appropriate patient," says de Bustamante.

No more blanket coverage

One plan taking a harder look at orphans is not-for-profit MCO Healthfirst. The organization, sponsored by hospitals and medical centers in New York, offers low-cost or free plans for those on Medicaid, Medicare Advantage and on the state's health benefit exchange.

Jay Schechtman, SVP & chief medical officer for the MCO, noted at NYBIO that he used to go years without seeing an orphan-disease drug claim. Now, he says they're becoming a major cost category.

Every quarter, "I have people from the finance side and our hospital saying, 'I don't understand—how can a single patient be on a $400,000 drug, and how can our entire loss from our book of business be two or three patients?' So it has become a very significant factor."

Moreover, Schechtman observes the emergence of a "new category of orphanised diseases," encompassing the most severe aspects of common chronic ailments. That is, something may not be an orphan disease but can be "orphanised" by finding the smallest cohort of patients that will offer the most compelling value-for-money argument.

There are two sides to the trend: Critics would say companies are creating a classification and a need where one did not exist before—a practice they may see as self-serving at best and irresponsible at worst. Supporters might say industry is being responsible in targeting its drugs with specificity—to the population where the medicine will work—and, as opposed to unleashing expensive medicines on

Orphan launches also prone to pitfalls

"If there is a need for an orphan drug, it should sell well," says research firm EvaluatePharma. But the market has become more competitive. "There is an increased trend toward 'me too' indications and label extensions on existing marketed drugs." This can lead to pushback from payers or regulators. An evaluation of the successes and pitfalls of recent orphan therapy launches shows it's not always smooth sailing for these drugs when they reach market. (Selections based on information from EvaluatePharma, CB Partners and other *MM&M* research)

KALYDECO

Kalydeco, Vertex Pharmaceuticals' roughly $300,000-a-year (US) drug for cystic fibrosis (CF), is considered a prime example of a well-developed product with a well-defined population. Good surrogate endpoints within patients showing specific gene mutations helped pinpoint the treatment population and the budget impact for payers. Since launching in 2012 the drug has seen rapid uptake in the US and key markets including Germany, France and England. Garnering strong support from CF advocacy groups, Kalydeco has since been shown to work in other gene mutations. The firm estimates 2014 sales at $470 million to $500 million.

KYNAMRO

HoFH shot Kynamro hit the US market in 2013, after a non-unanimous Adcom vote, with a price of $176,000 per year. About a month before, Aegerion's $295,000 pill Juxtapid was approved for the same condition. Both drugs require REMS. But even with its lower price point and more convenient once-weekly dosing, Kynamro seemed fated to be a tier-2 product behind the oral. Sanofi's Genzyme unit, which co-developed Kynamro with ISIS, has not released revenue numbers, but Sanofi was said to be adding sales reps, a sign the launch has been slow. Meanwhile, Aegerion drew a subpoena from the DOJ and an FDA warning letter for its CEO's comments in an interview. But Juxtapid reported 2013 sales of about $48 million and forecasts 2014 sales of $190 million to $210 million. Kynamro has also had trouble going global: Europe has twice rejected it.

MAKENA

Makena, approved by FDA in 2011 to reduce the risk of preterm birth, shows how an orphan launch can go wrong. Preterm labor can be costly to a health plan, so marketer KV Pharmaceuticals (which has rebranded as Lumara Health) anticipated little payer resistance. But it ran into obstacles. The first, an uproar over its price: $1,500 for a weekly injection, when compounding pharmacies had sold it for $10-$20 a dose. The FDA said it would not clamp down on compounders. Bowing to pressure from medical groups and two senators, KV reduced the Makena price by 55% to $690 per injection. It later entered Chapter 11 bankruptcy and ended up the target of a lawsuit by Hologic, which had sold KV rights to the drug contingent on royalties, for what Hologic charged was inept marketing.

SOLIRIS

A "top pick in terms of impact on a single company and publicity surrounding the orphan space," according to EvaluatePharma, Alexion's Soliris was FDA-approved for paroxysmal nocturnal hemoglobinuria (PNH) in 2007. A second indication, atypical hemolytic uremic syndrome (aHUS), came in 2011. The drug is now a blockbuster, and PNH and aHUS are forecast to achieve global sales peaks of about $2 billion each. While Soliris lists for $440,000 a year in the US, in the UK, European regulators have taken a tougher stance. Last year, a UK health minister threw out an advisory panel's positive recommendation for Soliris's aHUS indication, referring review to UK price watchdog NICE. And this past March, NICE asked for more information on why the drug costs so much.

Flying the global P&R pathway

NPS Pharmaceuticals has been selling Revestive, approved for the ultra-orphan disorder short bowel syndrome (SBS), on a per-patient basis in Europe but plans to go through each country's formal reimbursement process this fall (in Europe, approval is centralized, but each of the 30 member states has its own practices for reimbursement).

To secure coverage, developing the value dossiers is "absolutely critical," says Eric Pauwels, president of NPS Pharma International, which negotiated back the ex-US marketing rights for Revestive in March 2013.

Companies must first work to understand how they will sequence the submission of dossiers to obtain the highest price and reimbursement based on the clinical data they have, and with what type of value messages. They must define the burden of illness and how they will be able to impact costs.

Because Revestive's value has to do with decreasing patients' dependence on IV nutrition, the firm has had to examine the infrastructure of each country in managing intestinal failure and SBS.

"We prepared dossiers and [will] sequence launches according to where we believe we will have the best possible chance of establishing a price and getting access and reimbursement within a fairly narrow corridor, and comparable to the US price," says Pauwels.

Germany, the UK, the Nordic countries and France are among the countries it's targeting.

If the committees in each country assign a high benefit rating, that bodes well. "The next step is, when people who hold the envelopes for budgets ask us, what does the G-BA [in Germany] or NICE [in England] or HAS [in France] think about the product," Pauwels explains, "if it's a high rating, we are in a better position to negotiate a price that we think will be more sustainable."

As orphan policies evolve in various countries, they have not always translated into differentiated pricing & reimbursement policies. That's an issue as orphan diseases, due to their low prevalence, face unique challenges in development, pricing and reimbursement that indicate they should be assessed differently (see main story).

As a result, according to pharma consultancy CB Partners, orphan drugs have struggled to obtain positive reimbursement decisions in areas like Scotland and Poland. Likewise, Argentina, Mexico and Brazil have yet to create a distinct P&R pathway.

the general population, is restricting the need and reducing waste.

One company that counts itself firmly in the latter camp is Conatus Pharmaceuticals. The clinical-stage biotech's lead candidate, emricasan, has orphan designation and is in Phase II for treating liver-transplant patients with fibrosis. As it builds its commercial approach, Conatus is planning to incorporate outcomes into upcoming studies, says CEO Dr. Steven Mento.

"We're not looking for large populations of patients who will take it forever," Mento tells *MM&M*. "We're focusing on sicker populations where there is a value proposition for physician, patient and payer."

To that end, he says Conatus is testing the drug's activity against a known biomarker and, once it determines the right analysis (based on potential payer response and other factors), it will look to carry out that analysis in Phase III.

Even so, insurers may be wary of such an approach. "If a drug comes out for ALS, I'm going to be very happy," says Healthfirst's Schechtman. "But we're not just going to blanketly accept as we used to and say, 'ALS is an awful disease, let's cover it.'"

The payer's orphan-drug tool box also includes tiering and costing. Healthfirst has also turned to cheaper "preferred" therapies in some categories, mainly those with competition. And after initial pushback from patients and families, they've been accepted, and the plan is saving hundreds of thousands of dollars a year, Schechtman says. "I don't agree with it, but patients are going to have to pay more."

It's also working on individualized treatment plans with doctors: "We can't just say the patient has the diagnosis, they should get the orphan [drug] and just approve it based on the FDA. We're going the extra step and having a discussion with the physician."

Especially in some orphan conditions, it's using prior authorization, and the big arrow in its quiver: asking for re-authorization and demonstration of response—"Why keep a patient on a drug for two years if after six months they've shown absolutely no response," he says.

'This isn't oncology'

"The end result," says Schechtman, "is, this isn't oncology. We have actually a freer hand than in oncology…for now at least, we have the regulatory authority to make some decisions on this. We fully agree there are patients in need, there are tremendous gaps in care, but the pricing and the number of these therapies has become a significant issue."

By no means is that the only challenge facing marketers. Regulatory hurdles are higher, too—the FDA isn't allowing sponsors to get away with as few subjects in orphan-drug clinical trials any more. And as companies proliferate, the hunt for sales-force and marketing talent with rare-diseases experience is getting more competitive.

But the expected budget impact from orphan drugs and the trend toward ever tinier biomarker-driven classifications loom largest, at least for insurers. Orphan drugs are expected to account for 16.8% of total drug spend by 2020, based on forecasts and total brand sales, up from 10% in 2012, according to research firm EvaluatePharma.

"Over the last 10 years, things have changed quite a bit in payer marketing," Pauwels says. "There's increasing pricing pressures, increasing demand to show you have a strong value proposition."

Does this spell trouble for drugmakers? Maybe, but that challenge is not specific to this sector. "I think it's becoming more and more challenging, whether you are orphan or not," adds Pauwels.

Improving orphan access

One step biotechs can take to improve orphan access involves early involvement of health economics and outcomes research (HEOR) activity in the clinical R&D stage, similar to what Conatus plans to do in Phase III. According to CB Partners, this can ensure proper development of instruments and modeling endpoints.

The need to show proof of value "is always the case right now and will not go away," adds Mento, the Conatus CEO.

According to Pauwels—who's hoping to be able to launch Natpara (Adcom panel tentatively scheduled for 7/24/14) and Phase II candidate NPSP795 for autosomal dominant hypocalcemia with hypercalciuria (ADHH)—the biggest predictor of coverage success is innovation.

And even then, it's only somewhat reliable. The definition is not standard the world over. Incremental advances on existing rare-disease drugs, for instance, are often subject to price-referencing overseas. "The value proposition for reformulations and international pricing really isn't there," he says, which is why these tend to be US-centric products. But innovation is still rewarded. "With the US market, if you have innovative products, that's the key." ■