Pharma's Orphans
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Ron Bartek, FARA

Ron Bartek had never heard of Friedreich's ataxia (FA) in 1998 when his stepson Keith Andrus was diagnosed with the rare genetic disease at age 11 after three fearful years in a medical wilderness. "My wife called me right after leaving the neurologist's office, crying like a baby," he recalls. "I asked, 'Well, what pill does he take?' and she said, 'There's no pill, no treatment, nothing.'" That night, the Barteks shared a chair searching the Web for information about the disease. "We saw all the bad news—the horrific prognosis and not even any research into possible treatments," Bartek recalls. Friedreich's ataxia is a degenerative disease, targeting mainly nerve cells and the heart muscle; many patients die in early adulthood, but not before losing the ability to walk or talk or worse. "The only hopeful information was that a year earlier, the gene that caused the disease had been identified," says Bartek. "We thought, 'If we can start an organization, maybe we can get a drug based on that.'"

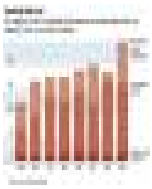
Nowhere does drug development get more personal than in the world of orphan diseases. Some 7,000 rare conditions have been designated by FDA as "orphans"—they have not been "adopted" by pharma because the patient population is too small (200,000 or less) and the R&D investment too big to be sufficiently profitable. As many as 80 percent are hereditary childhood conditions. Our much-touted free market leaves the 25 million Americans who suffer from these diseases out of luck.

Yet the imperative to literally save their child's life has transformed thousands of parents into activists, even if their strategy and style are far more accommodating than the militant, media-savvy demonstrations of their AIDS activist forbearers. From the Abetalipoproteinemia Collaboration Foundation to the Zellweger Baby Support Network, desperate parents like Ron and Raychel Bartek who refuse to take no for an answer have mobilized to put a rare disease on the map. And with the advent of venture philanthropy, a growing number are investing their hard-won charitable dollars in the discovery and development of drugs.

Now, 12 years after founding the Friedreich's Ataxia Research Alliance (FARA), the Barteks keep a watchful eye on the progress of 17 experimental FA drugs, including six in clinical trials—a somewhat improvisational pipeline that owes its existence mainly to FARA's own initiative. "Now we can tell a newly diagnosed patient, 'You can get on the registry and be eligible for the first drug in trials,'" he says. (In photo below, Ron and Keith are at Ride Ataxia Philadelphia in October 2009.)

Big Breaks for Little Diseases

The Orphan Drug Act was passed by Congress in 1983 to coax the drug industry into the rare disease space. The law offers a raft of incentives, including a tax credit equal to 50 percent of the clinical trials' cost, priority review at FDA, no PDUFA fee, and, most enticingly, seven years of market exclusivity.



Seeking Approval: The regulatory road is challenging to get approval for orphan drugs, which are designed to treat rare medical conditions

The legislation is almost universally viewed as a roaring success. Since its passage, FDA has approved 353 orphan drugs and granted orphan designations to more than 2,116 compounds. A report in January by Christopher Milne at the Tufts Center for the Study of Drug Development found that even after more than 25 years, the trends in orphan drug development are up. One third of all FDA approvals between 2006 and 2008 were orphan drugs. Revenue from orphan drugs in the US reached $32.5 billion in 2006, more than half of the entire market; sales are set to grow to $50 billion by 2011, an 8 percent jump. Such statistics contrast vividly with most industry trends—a fact that has not escaped Big Pharma, whose share of all orphan approvals leapt from 35 percent in 2000-02 to 56 percent in 2006-08. (For a more detailed breakdown of orphan drug and designation trends, see chart.)

Novartis has long been Big Pharma's lonely leader in this space, with four orphan drugs on the market, including the tyrinose kinase inhibitor Gleevec, which brought chronic myelogenous leukemia (and related rare cancers) to heel. Approved in 2001 after clinical trials that broke all records for speed, the "magic bullet" had originally been shelved, the victim of a marketer's "too small" mentality, until a Web-driven protest by CML patients helped the Swiss pharma see the light. Now a $5 billion blockbuster, Gleevec is both a cautionary tale for advocates and the envy of every orphan drugmaker.

Now Novartis has company. Most notably, GlaxoSmithKline launched a standalone business unit for orphan drugs in February even as it was shuttering several primary-care development programs. Last month, the British firm inked a deal worth up to $1.5 billion with Isis Pharmaceuticals, whose antisense platform is the granddaddy in the RNA-based therapy space. This follows the behemoth's $650 million agreement with Dutch biotech Prosena to take its antisense drug for the orphan disease Duchenne muscular dystrophy into Phase III.

Ironically, the emergence of the orphan space as a significant opportunity for pharma may have less to do with the incentives of the Orphan Drug Act than the necessities of the industry's radically upended market dynamics. With the collapse of the high-volume primary-care blockbuster model, companies are dancing as fast as they can to stuff their pipelines with high-margin specialty drugs. Not only are orphan drugs the ultimate niche product—they're also a state-protected monopoly free of price controls and generic competition, with guaranteed reimbursement and minimal marketing expenses. And they fetch some of the market's highest price. Orphan powerhouse Genzyme charges from $200,000 to $400,000 for its enzyme-replacement therapies for lysomal storage diseases such as Gaucher, Pompe, and Fabry.


Emil Kakkis, Kakkis EveryLife Foundation

These budget-busting bills are typically covered by insurance in the US because keeping small numbers of patients healthier for longer is more cost-effective than leaving them untreated and in need of frequent hospitalizations. Drugmakers try to remove some of the sting with patient-assistance programs where shortfalls and steep copays occur. Yet a child with an orphan disease requiring lifelong treatment can reach the lifetime cap in the family's insurance policy before hitting adolescence. As a result, the orphan disease lobby pushed hard for Healthcare Reform Bill's no-lifetime-caps provision. (They continue to fight against cost-effectiveness, seeing it as a serious threat to patients with orphan diseases that are treated only by off-label drugs.)

Working the System

The Orphan Drug Act has its holes and loop-holes, however. Only 200 of the 7,000 orphan diseases have become treatable in the 27 years since the legislation's passage. Pharma has pursued a predictably risk-minimizing approach to orphan R&D, often choosing to develop follow-ons in an already-trod disease rather than batting for breakthroughs in virgin territory. Celgene's thalidomide more than doubled response rates for multiple myeloma, a rare blood cancer, but its notorious safety profile made it vulnerable to potential follow-ons. Rather than plowing profits into a new disease, the drugmaker developed a second-generation version, while Millennium, targeting a different pathway, released Velcade. Several other potential treatments are in the works. Increased options are good for patients with multiple myeloma, but advocates for the many untreated orphan diseases can't help but regret what might have been. Whether increased direct competition among big pharmas will spur increased innovation in the space remains to be seen.

Of course, no drug developer can predict whether its compound will be a first in class, a follow-on, or a dud. "It's only in hindsight that you can say whether or not it's a wasted effort," says Tom Hemphill, assistant professor at the school of management at the University of Michigan/Flint. And by targeting the most prevalent rare diseases, "you could argue that pharma is trying to maximize its investment by helping the most people," he says.

Yet pharma has also craftily worked the system by focusing on common disease targets and pathways that may yield orphan drugs capable of accruing additional indications or off-label use in conditions with much larger patient populations. This "expansive" strategy most famously turned the neurotoxin Botox, one of the first products to receive orphan drug status (for two conditions characterized by uncontrollable eye blinking), into a blockbuster treatment for that grave pandemic disease, fear of wrinkles.

Rare cancers, which comprise 30 percent of all orphan diseases and are the fourth-largest killer in the US, also happen to be the leading therapeutic category in the orphan space—not least because oncology currently attracts the biggest overall industry R&D spend.


Tom Coté, FDA

While drugmakers salivate over the expanded label and profits of a Gleevec, critics like Rep. Henry Waxman, who co-authored the original Orphan Drug Act, slam the strategy as an abuse of the law's spirit. Similar criticism recently led the EU to alter its own orphan drug legislation, allowing regulators to shorten the 10-year market-exclusivity granted a drug whose profits from nonorphan indications are deemed unseemly, although regulators have yet to quantify how much is too much. Waxman periodically proposes a similar clawback amendment to the Orphan Drug Act. "There's talk of corralling some of the act's unintended consequences," says Rob Glik, an expert in pricing and reimbursement at IMS Consulting. "Recent industry promises to invest in orphan diseases in the developing world may serve as a good measure to counter that pressure."

Yet the overwhelming sentiment is, Why mess with success? "The act has been enormously successful, and it's continually expanding," says Dr. Tim Coté, the head of FDA's Office of Orphan Products Development. He allows, however, that minor improvements could be made, such as bringing the EU and US legislations into closer alignment. But Coté opposes EU-style market-exclusivity takebacks. "The point is that people with a rare disease are getting a drug. We aren't interested in penalizing a company for making big profits for other uses of the drug."

Just Another Day at the Office

Driven by a sense of urgency, advocates like FARA's Ron Bartek are increasingly entering the drug-development business. Venture philanthropy has emerged as a logical (if last-resort) weapon in the fight against rare diseases as a growing number of groups are investing in companies in order to advance innovative discovery projects—often bankrolled by their own fundraising—across the so-called Valley of Death, the lab-to-clinic passage where most such projects expire. The Cystic Fibrosis Foundation alone has helped fund more than 30 compounds, including sinking $75 million into Vertex Pharmaceuticals to advance two novel mechanism of action into human bodies.

When they started down this road 12 years ago, the Barteks had only one advantage: political connections. He was a lobbyist on Capitol Hill; she was the manager of Rep. Billy Tauzin's Washington, DC, office. Aided by Tauzin, they sprang into action, stopping first at the National Institutes of Health, where they met Dr. Giovanna Spinella, a pediatric neurologist in charge of ataxia research. "She became our guardian angel," Bartek says. Spinella gave them their first lesson in patient advocacy. "We told her, 'We're here to ask you for your help,'" says Bartek, "and she said, "No, you are going to help us. You are the ones to start the organization and teach us about Friedeirch's ataxia.'"

And so they did. The Barteks founded FARA, pulling in the field's three top researchers as advisors, including the scientist responsible for discovering the gene mutation. Soon they began to receive phone calls and emails from parents of children with the disease or patients themselves, hungry for information, community, and progress.

"We knew we had to do more than raise awareness and raise funds for research," Bartek says. "We wanted to get a drug as fast as possible—and that meant creating an entire infrastructure and collaborating with many different stakeholders." Eventually, FARA would boast a global

registry of more than 1,200 patients, nine clinical-research sites, an FA natural-history database, and a range of R&D-essential translational tools, including mouse models to screen drugs, cell lines developed from their patients' blood and tissue samples, and clinical endpoints and biomarkers for trials.

On the drug development front, a single French researcher was testing a compound called idebenone in FA patients with heart disease. Takeda held the patent. "Our scientific director called Takeda US to ask if we could borrow the drug to do research," says Bartek. "They said, 'You're a rare disease? We're not interested.'" So the Barteks turned to their pal Tauzin, who just happened to be chair of the House Energy and Commerce Committee. "Before we knew it, the company had donated all the drug they had left."

After the NIH agreed to sponsor the first-ever FA conference, they struggled to fill the room, digging up 88 scientists from around the globe who were doing research on anything related to FA. The conference next year will feature some 200 FA-focused researchers.

FARA's Grass-Roots R&D

As with many compounds with an orphan designation, idebenone was originally in development for a much larger disease (Huntington's) and, after failing, was left on the shelf. (Takeda tried, without much success, to market it over the counter as an anti-aging treatment.) The compound moved swiftly into clinical trials: With toxicology and pharmacokinetics studies already completed, much was known about dosing and safety; with a database of hundreds of FA patients eager to have at it, enrollment wasn't an issue. NIH's Spinella stepped in, launching the first study in patients on the agency's own campus. FARA then raised the money to pay for Phase II trials. When idebenone showed modest efficacy at slowing down cardiovascular degeneration, the Swiss firm Santhera Pharmaceuticals took notice, licensing it from Takeda and launching a Phase III trial. Canada gave the drug conditional approval last July, and if FDA follows suit, Santhera will begin marketing Catena, the first FA drug, next year. But that's a big "if": data from the US trial did not show statistical significance, so the drug's fate depends on results from the longer and bigger EU study.

In its first foray into venture philanthropy, FARA awarded Edison Pharmaceuticals, a startup biotech, a $3.4 million research grant followed by an investment of $1.1 million to advance its lead product, alpha-tocopherol quinone (A0001), a coenzyme Q10 analog. In the lab, A0001 is able to stop the destruction of mitochondria, the energy source of cells that is believed by most researchers to be the cause of FA's neurodegeneration. With NIH backing, the group joined with Edison and a leading researcher to conduct Phase I studies. New York–based Penwest licensed this star in FA's clinical pipeline and is running Phase IIb trials.

Unlike some advocacy groups investing in orphan drug R&D, FARA has made a point of diversifying its risk by placing bets on several different mechanisms of action at once. In addition to targeting mitochondrial function directly, FARA-funded researchers are advancing various other approaches, including trying to raise levels of frataxin, the critical mitochondrial protein that is partially lacking in people with FA, using erythropoietin, an iron chelater, and a synthetic version of the protein.

Excited by Scripps Institute research showing that a compound that blocks the Histone Deacetylase (HDAC) enzyme was able to target FA's mutant gene and turn up its frataxin-producing capability, FARA paid for efforts to design the most effective HDAC inhibitor, using its own cell lines for the tests. "This is our one near-term shot at getting inside the gene and increasing its productivity," he says. "If it works as well in patients as does in our mouse models, it could be profoundly therapeutic." With backing from FARA and the Muscular Dystrophy Association, Boston biotech RepliGen is refining the HDAC inhibitor further for a planned IND filing later this year.

Investing in drug development is, for FARA, little different from lending a drugmaker its patient registry, transitional tools, or other resources. "We may get a small percentage of market proceeds if a company gets to that point," says Bartek, "but we're in this for the drugs, not the money."

But the foundation has not completely abandoned advocacy's tradition of confrontation. When Santhera set the price of high-dose Catena in Canada at $100,000 a year, Bartek was furious, not least because FARA had done considerable heavy lifting for the drug. "We did the basic science and a lot of the clinical research," he says. "Santhera didn't have to invest a dime in anything but a six-month, 340-patient Phase III trial—using our own patients, doctors, and sites. Now some patients in Canada are reporting that their government insurance may fall short. "We have to make sure they can't turn around and price-gouge our patients," he says.

Red-Tape Chronicles

If there's consensus that the Orphan Drug Act has succeeded in spurring investment and innovation, there's also general agreement among advocates, drugmakers, and regulators that the enterprise must be made less risky, more predictable. For one thing, the approval rate—22 percent, compared to 16 percent for mainstream drugs—needs to increase if Big Pharma is to gamble on potentially breakthrough science. For advocates of a so-called ultra-orphan disease (6,000 patients or less), this issue is especially acute—fewer patients mean fewer profits. A mere 14 percent of all orphan drug approvals since 1983 have been for these very rare conditions. The average patient population for an orphan drug is estimated at 75,000. Because the current system plainly favors the bigger orphan diseases, the "ultra" activists are pushing for sweeping reforms. The status quo is pushing back. This debate reveals one of the few tensions in a community otherwise ruled by uncommon civility and unity.

Dr. Emil Kakkis is the new kid on the orphan activist block. "We don't have to blow everything up," he says. "We can just make some very targeted fixes, like in 1992 with accelerated approval." Kakkis is the founder of Kakkis EveryLife Foundation, a new advocacy group for ultra-orphan drug development whose aptly named Cure the Process campaign takes direct aim at FDA. "Neither pharma nor other investors will invest in early-stage products unless they have a high probability of getting to market," Kakkis says. "But the science and rigor are being applied so stringently as to prevent that."

Kakkis argues that orphan drugs get second-class treatment at the hands of federal regulators. Of the 74 drugs that have come through accelerated approval, 65 are for HIV or cancer, while only

nine are for rare diseases. Fast-track approval (along with compassionate use and the introduction of surrogate markers in clinical trials) was an early victory for AIDS activists, who literally shut down FDA headquarters in Rockville, Md., in their effort to force the agency to cut the red tape. "The system has served HIV very well, turning a death sentence into a chronic disease in less than 20 years," says Kakkis. "I want to see the same progress in ultra-orphan diseases."

Kakkis has firsthand experience of system failure. As a fresh-faced post-doc at UCLA in 1995, Kakkis was one of the world's few researchers working on MSP-1, a fatal genetic childhood disease caused by an enzyme deficiency. He had succeeded in making a synthetic version of the enzyme but failed at finding funds for clinical studies. Finally the Ryan Foundation, a small group started by the parents of Ryan Dant, a boy with MSP-1, raised $1 million on the promise of Kakkis' science.

Doing clinical development at BioMarin, Kakkis ran into not only red tape but a "do-this-no-do-that" attitude that wasted precious time and money. Although the molecule hit its surrogate endpoints and showed clinical benefits in its Phase III trial, FDA required BioMarin to do a second trial, complete with a placebo group. Then the agency denied accelerate-approval status, although there was no treatment for MSP-1. "Our patients were showing clinical improvement, no question," Kakkis say. "If this drug didn't qualify, what is accelerated approval for?" When data from the second study showed that the drug hit one endpoint but only "came very close to" the other, FDA recommended against approval, asking for yet another trial. In January 2003, the advisory committee looked at the same data and voted unanimously for approval. "They asked us why we didn't use surrogate markers," Kakkis says. "Of course, we had—and FDA signed off on it, but then changed its mind." Kakkis helped steer two more enzyme-replacement therapies to market for BioMarin before leaving last year to fund his own nonprofit.

The goal of Cure the Process is to prevent such costly bureaucratic bungling. The changes it proposes in order to meet that goal may amount to more than a few tweaks, however. Most ambitious is the demand for a separate office at FDA to review drugs for genetic and biochemical orphan diseases, since their evaluation requires specialized expertise. Currently, orphan NDAs are reviewed by scientists in the relevant therapeutic category whose evaluations may not be informed by the correct orphan-drug criteria. "Ultra-orphan supporters have the problem that their diseases almost never make any market sense," Kakkis says. "A new division at FDA would send a strong signal to industry encouraging their development."

Kakkis also wants more flexibility in the clinical trial process, including new study designs and data analysis, since drug effects in a very small population of clinically diverse patients can prove slippery to capture. Also needed are new standards ("qualified" rather than "validated") for surrogate and biomarker endpoints, since many drugs for most unstudied rare diseases are currently disqualified from accelerated approval.

Ekkis' make-it-new energy may ruffle the feathers of the community's more seasoned advocates. "We're opposed to anything that might dilute the Orphan Drug Act by carving out a separate pathway for ultra-orphans. It's important that the community stick together—that's how we got the legislation passed in the first place," says Mary Dunkle, vice president of communications at

the National Organization of Orphan Diseases (NORD), the veteran lobbying and policy-making coalition. Yet strategy differences didn't stop NORD from partnering with Ekkis, along with 100-plus other patient and physician organizations, in his drive for reform.

So Many Ideas, So Little Time

FDA appears ready, even eager, to be pushed on the orphan-drug front. Long viewed as saddled with a bunker mentality, the agency is undergoing a dramatic course correction at the hands of its two activist public-health officials who are opening the agency to sunshine ("transparency and accessibility") and its many demanding stakeholders. In February, FDA created a new position of associate director for rare diseases to keep track of orphan drug NDAs as they move through the approval process—plainly a response to NORD's long-, often-, and well-articulated critiques.

Whether a new orphan drug review office is on the agenda is a matter of dispute. "We have obtained agreement with high-level officials at FDA that they will support the creation of a new focused review division for certain rare disease not well covered—if we can obtain an additional $10 million," he says.

Office of Orphan Product Development head Tim Coté has a different version. "The science itself doesn't support it. Most orphan diseases do share certain technical problems like the design and recruitment of clinical trails. But as diseases, they cut across every medical specialty," he says.

Coté, for his part, is hitting the road with workshops for aspiring applicants in Orphan Drug Designation 101. "It's fairly radical for the agency to go out and speak directly to sponsors and have them generate submissions on site," he says. "We are trying to demystify the process for researchers who have a fire in the belly about their project but may not even know what 'IND' stands for." The first workshop, held in February at the Keck Graduate Institute in Claremont, Calif., drew 29 sponsors; four designations have already been granted from the crop of applications. A second workshop is set for August. Coté is also paying visits to top-10 drugmakers, reminding them that little diseases have large unmet needs. "I really hope to start seeing results soon," he says. "Getting orphan drugs to market reflects well on the industry and the agency."

Keith Andrus died of cardiac arrest in January. The brown-haired, blue-eyed, much-tattooed patient-activist was 24. In March, departing PhRMA chief, Billy Tauzin, paid a tearful tribute to Keith during his own farewell speech, screening a short film of Keith's too-short life movingly narrated by Raychel Bartek. "We always knew Keith would be on the cusp—either the first generation with a treatment or the last generation without a treatment," Ron Bartek says simply. Is his son's death a moment to take a break, step away from his nonstop activism? No. "This stopped being just about Keith the day we started," he says through tears.