

Crafting a Robust Business Model for Orphan Drug Development

AS RESEARCH INTO DRUGS targeting rare or “orphan” diseases has stepped up in recent years, so too has the need for a robust business model capable of bringing promising orphan drugs into the marketplace.

The earliest step took place in 1983, when President Ronald Reagan signed into law the Orphan Drug Act. More than a quarter-century later, the orphan disease community is looking again to Washington for help. U.S. Sen. Robert P. Casey, Jr. (D-PA) has introduced the “Creating Hope Act” (S. 606), which would enable drug developers who submit an orphan drug for review to receive a “priority review voucher.” The voucher would allow expedited review of another drug candidate, as with vouchers now issued for drugs that treat tropical diseases under the Food and Drug Administration Amendments Act of 2007. The bill would also allow vouchers to be sold or transferred more than once, and add “Chagas Disease” to the classification of tropical diseases. Creating Hope Act has been referred to the Senate Committee on Health, Education, Labor, and Pensions.

Also awaiting action is the Medical Foods Equity Act (S. 311) introduced by Sen. John F. Kerry (D-MA). The bill, referred to the Senate Committee on Finance, would require “medically necessary” foods and supplements, plus the medical equipment and supplies to administer such foods, to be covered by private insurance and four government programs: Medicare, Medicaid, Children’s Health Insurance Program (CHIP), and TRICARE.

“Experience has shown these treatments work, but patients are not always getting access to them,” said Mary Dunkle, vice president for communications with the National Organization for Rare Disorders (NORD). “Sometimes the argument is made that these are not drugs, they’re foods. But they’re medically necessary, so we’re trying to get the patient groups together. This issue also has to do with how FDA defines medical foods, with medical coding and with just trying to pull together the payers, and get everybody to come to the table.”

Three existing laws benefiting orphan drug development are up for reauthorization next year—the Best Pharmaceuticals for Children Act, the Pediatric Research Equity Act, and the Prescription Drug User Fee Act.

“While these aren’t expressly orphan disease pieces of legislation, the fact is that most pediatric diseases are orphan diseases,” said Nancy Goodman, founder and executive director of Kids v Cancer, a nonprofit group promoting pediatric cancer research. “As they are renewed, the community is looking at different ways to modify or improve them, so we can have greater impact.”

Emil Kakkis, M.D., Ph.D., CEO and president of Ultragenyx Pharmaceutical (Novato, CA), and president of the Kakkis EveryLife Foundation, said lawmakers should also streamline the FDA’s orphan drug review process. Drugs to fight rare diseases could be developed and brought to market faster, Kakkis argues, if the FDA would:

- Organize drug reviewers in more consistent smaller groups that manage particular functions: “We would actually end up getting a better quality review, because we would have people who are focusing in and becoming expert in particular areas of drug development, and particular disease or therapeutic areas.”
- Issue guidance that is more flexible in the use of alternative clinical designs and study analysis, to assure the best designs and analyses are being undertaken to capture data in more chronic, heterogeneous and difficult diseases.
- Accept surrogate endpoints “that are more than simply requiring a lot of clinical data, but in fact using the science we have and other information and not requiring a lot of definitive clinical data in order to use the marker.”

The fewer the regulatory hoops, Dr. Kakkis added, the lower the cost of developing new treatments, hence the lower their ultimate cost to patients. Enzyme therapies, depending on the size of the patient, can range from \$200,000 to \$500,000 a year, with the average around \$300,000. For the largest patients or those on particular drugs, the expense could climb close to \$1 million/year.

By contrast small molecule drugs—such as Kuvan, a treatment for the genetic disorder PKU—are in the range of \$75,000 to \$150,000, depending on size of patient and dosage needed. Some older simple drugs can cost less at about around \$30,000 a year, but some are less effective and/or harder to administer or tolerate.

“If people are taking financial risks, there’s expected return, otherwise there is no investment made. That’s the nature of the drug development business. However if you can lower the scale of financial risk, then you can lower the scale of financial return, and just take the whole structure down to a different level. I think that makes sense if we can do it in a scientifically sound way.”

The financial risk has risen as companies have needed more time and money to conduct research and shepherd orphan drug candidates through FDA’s approval process.

“The challenge right now is that drug development occurs in private industry in the United States. That’s where most of

our human capital is. And the challenge there is that private pharmaceutical companies have fiduciary duties to their shareholders to maximize profits. So it's very tough for them to go into niche markets like rare diseases markets, and the question is, what can we do?" Goodman said.

One solution, she said, would be to add incentives above those of the Orphan Drug Act for disease markets of 20,000 or fewer patients. A patient population of 20,000 would be among the larger ones for an orphan drug. Roughly 80% of rare diseases affect fewer than 6,000 patients in the U.S., according to the Pharmaceutical Research and Manufacturers of America (PhRMA).

"Because of these small patient populations, it can be nearly impossible for biopharmaceutical research companies to enroll enough clinical trial participants to meet the Food and Drug Administration's demands," said Lori Reilly, vice president with PhRMA. "Similarly, clinical trials require medical experts, and many little-known diseases do not offer a wide selection."

Reilly said the balance needed between patient access and safety can be particularly difficult to evaluate when a rare disease, left untreated, has devastating or fatal consequences: "Because of these and other challenges and burdens, rare disease R&D can be significantly more expensive and time-consuming than other biopharmaceutical research."

Rising research costs also explain the shift of recent years in who develops rare-disease drugs. During the first two decades of the Orphan Drug Act, treatments were developed and marketed by biotech startups that grew into corporate giants, such as Celgene, Genzyme, Shire HGT, and Kuvan developer BioMarin Pharmaceutical, where Dr. Kakkis worked from 1998–2009, the last three years as chief medical officer.

More recently, big pharma has taken a growing interest in developing drugs for rare diseases. At the 47th Annual Meeting of the American Society of Clinical Oncology (ASCO) in June, Novartis presented results of two Phase II studies for investigational Janus kinase (JAK) inhibitor INC424 (ruxolitinib), which it licenses from InCyte. The studies showed significant spleen size reduction and symptom improvement in patients with myelofibrosis compared to placebo at 24 weeks, and significantly reduced enlarged spleen size compared with best available therapy at 48 weeks.

In April, AstraZeneca began selling the orphan drug vandetanib to U.S. patients for the treatment of medullary thyroid cancer that cannot be removed by surgery or has spread to other parts of the body. "AstraZeneca strives to meet patient need whenever we can, with differentiated and targeted medicines that offer patients real medical benefit, and this includes the potential future launches of other orphan drugs," AZ spokeswoman Laura Woodin said. GlaxoSmithKline joined Prosensa (Leiden, the Netherlands) in January to start a Phase III trial of a drug to treat Duchenne muscular dystrophy (DMD), while GSK and Pfizer launched rare disease units last year.

"They [big pharma] have this capability now that they are global enterprises, so their markets are not just here in the United States, but they're in Latin America. They're in Asia. They're in Europe. It is a globalization of the companies, and as a result there is a globalization of efforts to meet the needs of the rare diseases community," said Stephen C. Groft, Pharm.D., director of NIH's Office of Rare Diseases. "You have a market not only in the United States, but throughout

the world. And I think that's a tremendous possible expansion of products."

Dr. Kakkis says big pharma's growing presence in developing orphan drugs also reflects the waning desire of venture capitalists to invest in biotech startups because of the long time required for returns on investment.

"But pharma, being a strategic investor, doesn't mind having a five-, six-, or seven-year timeframe. They're going to fill their pipeline by picking up these assets," Dr. Kakkis said. "The problem is, will they actually be able to develop them? And what kinds of products are they going to pick? Will they really be ultra-rare? More likely, they're going to be the more common of the rare disorders, but we don't know for sure how it's going to play out yet

"You could say, well maybe that's fine. But it's not. What they're doing is cutting all these people in R&D, outsourcing research to these little companies and things they are acquiring. In the meantime, the total amount of R&D in drugs is dropping dramatically, which is going to mean less drugs and less effective treatments down the road," Dr. Kakkis added.

One avenue to keeping smaller drug developers engaged in rare disease research, Groft of NIH said, will be to help them partner with other entities through the proposed National Center for Advancing Translational Sciences (NCATS). Promoting collaborations and accelerating development of new drugs in research areas of high need but limited commercial appeal is among purposes of NCATS, which would also oversee the \$24 million Therapeutics for Rare and Neglected Diseases (TRND) program. But uncertainty over the budget has clouded the outlook for NCATS opening as planned with the Oct. 1 start of Fiscal Year 2012.

Groft cited two successful models in which researchers have united with corporate and patient advocate partners to develop orphan drugs.

The Urea Cycle Disorders Consortium consists of doctors, nurses, genetic counselors, research coordinators and research laboratories committed to carrying out clinical research into causes and treatment of urea cycle disorders (UCD). The consortium works together and in close collaboration with the National Urea Cycle Disorder Foundation, the national patient advocacy organization, which has connected physicians and patients to advance research in the disorders.

The consortium's principal investigator, Mark L. Batshaw, M.D., received funding from NIH's Office of Rare Disorders Research and the Eunice Kennedy Shriver National Institute of Child Health and Human Development to become a founding member of the Rare Diseases Clinical Research Network in 2003. The consortium in 2009 won \$6 million from the network to continue the research—\$1.25 million a year for five years.

"We were fortunate enough to get to almost double our grant support through additional philanthropic support. That allowed us to gradually increase the number of consortia sites from the original five to the current 15"—12 in the U.S., two in Europe, and one in Canada, said Batshaw, who is executive vice president and chief academic officer for Children's National Medical Center (Washington, D.C).

That allowed the consortium to recruit many more patients than it initially planned. Patients came primarily from already established genetic metabolic centers, as well as referred from the National Urea Cycle Disorders Foundation.

“Between those patient groups and our individual metabolic centers, previously the largest study that had ever been performed on urea cycle disorders had about 20 individuals in it. We now follow 500,” added Batshaw, who is also director of Children’s National’s Children’s Research Institute. “When you have that many patients, you can start asking really important questions in terms of data mining of what the outcome is going to be, in terms of cognitively, and what are the precipitants for metabolic crises in these children, and what’s the effect of vaccines on these children, and lots of other questions that become very important.”

The sizeable number of patients made the consortium large enough to carry out multiple drug trials. That sparked interest from pharmaceutical and biotech companies, who saw value in a large, homogeneous group of patients followed longitudinally on a single clear clinical pathway. Also attractive was the consortium’s NIH funding and commitment to support their drug candidates during FDA reviews.

“Where there were very few pharmaceutical/biotech companies in the space of urea cycle disorders, now we’ve added about five new drug companies just in the last two to three years who are either doing drug studies with us, or are contemplating doing that,” Batshaw said.

The consortium helped Orphan Europe (Paris, France), part of the Recordati Group, win FDA approval for N-carbamylglutamate (Carbaglu®), designed to treat N-acetylglutamate synthase (NAGS) deficiency. The consortium is also working with Cytonet (Weinheim, Germany), which on May 17 won FDA orphan drug designation for its liver cell infusion of donated human liver cells for the treatment of UCD in young children. Cytonet will pursue a multicenter clinical trial to evaluate the safety and efficacy of its liver cell therapy in infants to children up to age 5 with UCD. Another consortium-backed company, Hyperion Therapeutics (South San Francisco, CA), won FDA Fast Track designation last year for its investigational compound glycerol phenylbutyrate (HPN-100) for chronic management of UCD.

Groft also cited the Parent Project Muscular Dystrophy (PPMD), a national not-for-profit organization founded in 1994 by parents of children with Duchenne muscular dystrophy (DMD) and a variant, Becker muscular dystrophy. PPMD maintains a portfolio of investments in drug developers with products aimed at rare diseases.

PPMD awarded \$40,000 in April to SomaLogic (Boulder, CO) and Cincinnati Children’s Hospital Medical Center (Cincinnati, OH) to use SomaLogic’s proprietary screening technology to identify biomarkers for DMD. PPMD has also awarded \$1 million under an initiative to address cardiac issues in devel-

oping new therapies—\$750,000 to Ronald G. Victor, M.D. of Cedars-Sinai Medical Center (Los Angeles, CA) to study phosphodiesterase inhibitors (sildenafil and tadalafil) as a possible therapy for DMD; and \$250,000 to PTC Therapeutics (South Plainfield, NJ), with potential for more, toward a new treatment that improves heart function in patients with Duchenne/Becker muscular dystrophy (DBMD).

PPMD and PTC are partners in “Project Catalyst,” focused on discovering and developing new therapies for DBMD. PTC won \$15.4 million from NIH in 2007 for the program, which began with \$3 million from PPMD and has leveraged another \$3 million in private funds.

“With a rare disorder, you’re raising from a relatively small pool of people, especially when you match that up against the numbers that people throw around for the cost of drug development. The idea for PPMD is, if we invest, where’s the follow-on funding? What happens next?” said Pat Furlong, PPMD’s founding president and CEO. “We look to how can we use both our investment as well as our advocacy to partner these investments, to attract industry, to provide opportunities, both for NIH funding and for industry funding through NIH or SBIR vehicles.”

PPMD also collaborates with NIH to provide “End Duchenne” grants to researchers while they gather data likely to improve their chances for larger NIH grants. In one such “bridge” grant in 2009, PPMD gave \$200,000 to Krista Vandeborne, P.T., Ph.D., chair of the University of Florida’s Physical Therapy Department, toward work with MRI and MRS technology. The work enabled her to win a five-year, \$7.5 million grant last year from NIH’s National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS) and the National Institute of Neurological Disorders and Stroke (NINDS).

In a typical year PPMD funds a combined \$1.5 million in End Duchenne grants. “We bridge basically up to 80% of the year’s requests through NIH,” Furlong added.

Funds for research, together with relationship-building by advocacy groups, are essential if the number of orphan drugs is ever to catch up to the number of rare diseases they are meant to combat. So too are strengthening the Orphan Drug Act, and reforming regulations so new therapies can get to patients faster and at less cost.

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