Rare Diseases and Orphan Drugs Lift Pharma Innovation

As hundreds of candidate drugs receive official “orphan” status, the Orphan Drug Act gets re-examined. Meanwhile, these drugs are driving the growth of specialty pharmacy  By Suzanne Shelley

There are now 357 commercialized orphan drugs approved by the pathway outlined in the Orphan Drug Act of 1983 (ODA), with hundreds more receiving that status in clinical research phases. On one hand, that number can be looked on as an unqualified success—many of these drugs are offered for rare diseases affecting (by regulatory definition) 200,000 patients or fewer in the US, or fewer than 5 per 10,000 patients in Europe. On the other hand, advocates for nearly 5,800 other rare diseases for which cures or treatments have not been commercialized are petitioning Congress to compel FDA to loosen the review and approval process, and provide even more incentives for manufacturers to develop new treatments.

Equally significant, ODA status can help a struggling young biotech company to get a novel treatment method into commercial use; in some cases, the orphan drug status becomes the springboard for opening up a molecule, biologic or treatment to larger, non-orphan conditions. And now, Big Pharma is becoming enthusiastic about pursuing rare diseases, with companies such as Pfizer and GSK setting up orphan drug programs.

A high proportion of orphan drugs are also specialty pharmaceuticals (60% are biologicals), requiring close coordination with providers (such as for infusion therapies), and extensive patient support. This, in turn, is spurring the development of specialty pharmacies and specialty distributors to provide the hands-on service necessary. In some cases, specialty pharmacies, together with researchers and healthcare providers, help organize registries of rare-disease patients (who are often poorly diagnosed precisely because the condition is so rare), which in turn helps assemble the clinical-trial group to move the research process forward.

Today, the bulk the 6,000 rare diseases that have been identified — 83% — are believed to affect fewer than 6,000 patients (each) in the US. “From a business development and venture capital perspective, with such small patient populations, the pressure is on to bring these products to market quickly, to address patients’ unmet needs and give the sponsors and investors a chance to recoup some of their investment,” says Craig Kephart, president and CEO of Centric Health Resources (Chesterfield, MO). Centric has pioneered commercialization in the “ultra-orphan” drug category—diseases with fewer than 20,000 potential patients.

Juicing a company prospectus

Drug developers seeking ODA status for their development programs travel a well-trodden path. Just in the past month or so, FDA has granted the designation to these firms:

- Amsterdam Molecular Therapeutics Holding NV (Amsterdam, Holland) will test AMT-080, a gene therapy for Duchenne muscular dystrophy. Amsterdam’s technology, known as adenoassociated viral-vector (AAV) technology, is being evaluated for other rare diseases, and Parkinson’s disease as well.

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- BioMarin Pharmaceutical (Novato, CA) won ODA status for BMN-701 for Pompe disease, which interferes with muscle development.
- Athersys, Inc. (Cleveland) will develop its multipotent adult progenitor stem-cell therapy, called MultiStem, for graft vs. host disease (GvHD) in bone marrow transplants for blood-borne cancers. Pfizer is working with Athersys on other GvHD conditions.
- Catalyst Pharmaceutical Partners (Coral Gables, FL) is developing CPP-115, a derivative of a compound called vigabatrin, and now has ODA status for treating epilepsy-like infantile spasms. Related forms of the compound are under development by Catalyst for cocaine and opiate addiction.
- Ziopharm Oncology, Inc. (New York) will investigate darinaparsin (brandnamed Zinapar) for the treatment of peripheral T-cell lymphoma (PCTL). The drug will be used in combination with a group of drugs called CHOP (cyclophosphamide, doxorubicin, vincristine and prednisone), which is the current front-line therapy for the condition.

For public companies, these announcements routinely cause an uptick in stock price—a nice boost in a generally volatile market for technology stocks—and in some cases, existing or proposed collaborations with Big Pharma are accelerated. More directly, ODA status can result in financial grants from FDA to the development company.

Big Pharma, which has selectively pursued orphan drugs in the past, is now getting its act together as well. Last February, GlaxoSmithKline announced it was halting research on drugs for pain and depression and launching a new standalone unit to research and develop therapies for rare diseases. “Despite the rarity of each condition, the number of diseases means that 6–8% of the population may be affected by some rare disease,” said GSK at the time of the announcement.

Through its new unit, GSK has already entered into strategic collaborations with Dutch company Prosensa to develop nucleic-acid-based therapies and RNA-based compounds. And through an agreement with Japanese company JCR Pharmaceuticals will develop bioactive products. GSK has also obtained the global rights to a number of enzyme-replacement therapies that could be used to treat Hunter syndrome, Fabry disease and Gaucher disease.

In March, GSK created a strategic partnership with Isis Pharmaceuticals (Carlsbad, CA), to tap into its RNA expertise and develop novel therapies via the Isis antisense drug-discovery platform, believed to be a direct pathway to addressing disease-causing proteins.

Pfizer has followed suit, forming a Rare Diseases Research Unit, based in Cambridge, MA, and started with its December 2009 purchase, for $110 million, of a license to a treatment (taliglucerase alfa) that is being developed by Protalix Biotherapeutics (Karmiel, Israel) for Gaucher disease, an inherited enzyme deficiency. It could compete with Genzyme’s Cerezyme, which can cost $200,000-$300,000 per year, and according to published reports is a billion-dollar product for that company. In September, it added to its portfolio with a bid to purchase FoldRx Pharmaceuticals, which has a treatment for a neurodegenerative disease known as amyloid TTR polyneuropathy (ATTR-PN), an orphan drug currently in Phase II/III trials.

“It’s likely we’ll see the pace of partnerships pick up between small companies that have the intellectual capital but no money and Big Pharma firms that have the commercialization expertise,” observes Centric’s Kephart.

Acquisitions are also a strategic move for smaller players, to help them increase their footprint in the orphan drug arena. For instance, BioMarin Pharmaceutical recently acquired Lead Therapeutics, a drug-discovery company specializing in rare cancers, and Huxley Pharmaceuticals, which owns the rights to a proprietary therapy to treat Lambert Eaton Myasthenic Syndrome, an autoimmune disease.

“From the patient perspective, we aren’t questioning motives,” says Peter Saltonstall, president of the National Organization for Rare Diseases (NORD; Danbury, CT). “We are simply glad to welcome any companies to the rare disease space who are seriously committed to developing safe, effective treatments for patients.”

The rare-disease attractors
FDA grants are but one part of the current ODA. The full program has these features and incentives:

- Up to 50% of the cost of clinical trials is defrayed in the form of tax credits, along with selective grants and financial assistance
- The customary Prescription Drug User Fee associated with all drug marketing applications is waived (this is typically more than $1 million per application)
- The approved orphan drug is given seven years of market exclusivity in the US and six to ten years in the EU (During this period, FDA is generally prevented from approving another company’s version of the “same drug for the same disease or condition,” and irrespective
of whether patents expire during this period, the regulatory agencies will hold off approving generic competitors
• An expedited review process, and flexibility when it comes to the quantity and quality of the evidence needed for an orphan-designated candidate product to receive FDA approval.

“Thanks to these ODA tax benefits, most drug developers can expect to write off about 40% of the costs of bringing these drugs to market,” says Kephart of Centric.

Meanwhile, the seven years of exclusive commercialization rights for the product “gives the company a monopolistic opportunity to make a profit that would be unavailable in other drug markets,” adds Amy Grogg, president of Xcenda (Palm Harbor, FL), a business unit of AmerisourceBergen Specialty Group.

The potential for a product to be fast-tracked for approval brings its own rewards. “This economy has absolutely crippled the venture capital market, especially for high-risk, biotech candidates. If it’s going to involve 15 years to bring a drug to market for 2,000 patients, that’s not a very attractive play for many venture capital investors, and such a scenario tends to discourage investment in this arena,” says Kephart. “Venture capitalists need to know how long it will take to recoup the development costs and get a decent return on investment.”

In 2009, nearly half (43%) of all new specialty drug approvals received the orphan drug status from FDA, and we believe this trend will continue,” says Steven Russek, RPh, VP and chief clinical officer at Accredo Health Group (Memphis, TN), a specialty pharmacy business unit of Medco Health Services. Beyond altruism, without these incentives, drug companies would have little impetus to undertake the long and risky process of pursuing medications for which the ultimate market potential was, by definition, severely limited.

Accelerated development

With approved ODA drugs, ODA drugs in the pipeline, and funds and incentives flowing from FDA to developers, what’s not to like? Patient advocates and manufacturers themselves would like to see the program opened wider. The current state of affairs still leaves 5,800 rare disorders — affecting 20–25 million Americans or more — without an approved drug therapy. “It seems as if the low-hanging fruit have been harvested,” said NORD chairman Frank Sasinowski, in Congressional testimony on June 29. “While much has been accomplished, much more remains to be done.”

The cost to develop any new drug is generally expected to be more than $1 billion. “The sad fact is that drug-development costs have very little to do with ultimate market potential, so orphan drugs must be priced much higher than, say, antacids or anti-depressants,” says David Lapidus, principal of market-research firm LapidusData LLC (Brookline, MA). “If drugmakers cannot recoup their development costs, and offer investors a competitive profit margin, affected patients will have no hope of treatment.” This creates an unconventional business model — one that requires a bevy of incentives and subsidies to help level the playing field.

The complaints about the current system boil down to: “a more predictable approval pathway for orphan drugs, including publication of promised FDA guidance on clinical trial design and new methods of statistical analysis, and a review of FDA standards used to determine the efficacy of rare disease products, taking into account the small patient populations involved,” says Grogg of Xcenda.

For a variety of reasons, designing clinical trials for orphan drugs poses its own challenges. For instance, the limited number of afflicted persons and volunteers available to participate in a trial will be limited. “When it comes to rare disorders…greater deference should be afforded the design of these trials and flexibility applied in the interpretation of their results,” Sasinowski of NORD told Congress last June. “If such a principle would be addressed and accepted by FDA, much good would come of it.”

Advocates are also calling on FDA to develop better guidance on the use of surrogate endpoints, and to develop suitable alternative statistical models that would allow researchers to reduce the trial size.

“Recognizing that for rare diseases, the clinical trial is going to be small because it’s hard to recruit hundreds of patients, many stakeholders encourage the greater use of surrogate endpoints — and a greater openness to follow the general philosophy to ‘study short and license long,’” says Kephart of Centric. “FDA is listening, and is showing great openness, but the agency is still struggling a bit on where to give on those pivotal issues.”

By way of example, FDA policy stipulates that the
minimum number of safety exposures to meet the statutory standard for safety for the agency to even accept a marketing application for review when the medicine is intended for a chronic condition is 1,500 persons exposed to the investigational therapy, with 300 to 600 of those exposed for at least 6 months, and at least 100 exposed for one year.

However, while the guidance does state that these minimum safety thresholds do not apply to therapies for rare disorders, it does not go on to formally state what would be required as an alternative. The agency “could have, for instance, stated an algorithm such as ‘at least 1% of the U.S. population with that rare disease must be exposed to the drug, with at least half of that group for one year,’” said Sasinowski of NORD. Instead, the guidance leaves it to the discretion of the FDA reviewers, to decide on a case-by-case basis — a practice that critics say leaves too much uncertainty, inflating the perceived risk and dampening the enthusiasm of both drug developers and investors.

Another challenge to orphan drug development is the inherent difficulty of identifying patients, let alone clinical trial participants—the diseases are, by definition, “rare” and often underdiagnosed. Here, the swift growth in patient or disease registries for rare diseases, often established by private advocacy groups, has been helping to make it easier and to identify patients. Once the product is in the marketplace, such registries also help manufacturers to more easily track patient progress, and gather the data needed to evaluate clinical effectiveness, safety and cost-effectiveness.

To further assist drug developers and reduce the trial-and-error nature of drug discovery, FDA’s Office of Orphan Products Development (OOPD) recently launched a new tool, the Rare Disease Repurposing Database (RDPD). The database identifies two types of drugs that are deemed promising for rare illnesses — promising investigational substances that have already received orphan-drug status and have been subjected to pharmacokinetic and toxicologic testing, and certain FDA-approved therapies that are already available for the treatment of some potentially related diseases. The goal according to FDA is to create “a far easier lift to drug developers than beginning with an untested new therapy compound.”

Specialty pharmacies: High-touch service

Most orphan drugs are high-maintenance products — both in terms of intense educational support that is needed for prescribers and patients, complicated distribution and administration protocols, and challenging reimbursement strategies, and in terms of complicated data-gathering that is required to monitor clinical effectiveness and safety.

As such, specialty pharmacies are typically called upon to provide high-touch service capabilities and bridge the gap between the drug maker and the target patients and physicians. “Many of today’s large specialty pharmacies are struggling to provide custom patient services within therapies involving a small number of patients who have high-touch service requirements,” says Dean Erhardt, principal of D2 Pharma Consulting, LLC (St. Charles, MO). This has led to the emergence of a niche sub-specialty within the specialty pharmacy sector.

Today’s specialty pharmacies are equipped with specialists and clinicians to provide not just nursing services to assist with subcutaneous injection and office or home infusion, but highly individualized guidance and coaching for patients and caregivers to improve drug adherence and manage side effects, and reduce co-morbidity and hospitalizations. This has the potential to improve outcomes and generate greater revenue for the drug makers, while reducing overall healthcare expenditures for the patient.

“Traditional pharmacy dispensing settings have many challenges in dealing with patients with rare diseases, and when the potential patient population is small, many healthcare providers simply do not have any experience in dealing with the complexities of managing the disease or the treatment,” says Mark Johnson, president of US Bioservices (Frisco, TX), a specialty pharmacy and business unit of AmerisourceBergen Specialty Group. “In fact, most of the products used for relatively rare, chronic diseases may have never been seen by pharmacists at traditional pharmacies.” He goes on to note that, “We often have to coordinate with insurance companies, nursing agencies, home care providers, physicians, manufacturers and financial assistance foundations to help our patients start and remain compliant with their prescribed therapies.”

“Because they deal in select disease states and complex chronic illnesses in small populations, specialty pharmacies become expert at managing those diseases,” says Pam Sauerwald, GM, Specialty Offering Development, IMS Health (Plymouth Crossing, PA). “Having the entire population of patients taking a given medication directed to one or two pharmacies allows these players to develop great experience and expertise.” She adds that, “For the physician, it’s probably a little less about educating the specialist on the disease and the drug than the ability to have the specialty pharmacy act as an extension of his or her office and field calls that would come to them if the patient were challenged with the therapy.”
And with the economies of scale that can result, “it can actually become less expensive from a sales and marketing perspective to market a high-cost product to relatively few physicians (potentially as few as a few hundred specialists), compared to marketing a low-cost product to a broader market of several thousand physicians,” adds Erhardt of D2 Pharma.

Similarly, “expensive stocking costs make many traditional pharmacies hesitant to stock these products, which creates an access problem for patients which can affect their quality of life,” adds Russek of Accredo Health Group.

Meanwhile, the direct-to-patient distribution model that results when drug makers partner with just one specialty pharmacy can help to eliminate some of the added costs and markups that typically arise along the way when there are multiple partners (and hence multiple touch points) in a more convoluted distribution channel. This shorter supply chain helps to minimize markups on these costly specialty therapies. And such centralization can provide drug makers with the data they need for the improved inventory control and better forecasting.

Payor pushback

Despite the fact that any given orphan drug can cost hundreds of thousands of dollars per year for a single individual, patients have, up to now, faced very little reimbursement pressure. Full coverage has generally been considered the status quo, partly because the limited number of ultra-pricey therapies and limited number of patients on any given insurer’s rolls tended to limit the overall economic exposure.

“However, in recent years, rapid growth in the number of premium-priced orphan drug launches, price increases, and new indications for existing products, coupled with increased pressure to curb healthcare costs, have forced many private and public payors to reevaluate their reimbursement schemes for many prescription products,” says Diana Dobrovolny, VP of integrated client development for InVentiv Advance Insights (Somerset, NJ).

“Today, there are more of these specialty products than ever before and new indications for some existing products. Each drug may have a limited patient population but with more and more of these premium-priced drugs on the market, things can really start to add up for insurers,” adds Rob Glik, senior principal, pricing and market access practice for IMS Health. He points out that on a strict pharmacoeconomic basis, many orphan drugs cannot be cost-justified by current assessment practices—which could leave patients with untreated conditions out in the cold.

“Patient access to orphan drugs is rarely denied, but these special products are not immune to the management tactics and benefit-design trends — such as greater cost sharing by patients (through, for instance, higher premiums, deductibles, variations in coverage by plan type, copayments, coinsurance, or annual or lifetime coverage caps) — that payors apply to other expensive biologics, injectables or specialty drugs, and in the absence of health policies that dictate otherwise, this trend is expected to intensify,” says Dobrovolny.

A survey of decision makers in 26 payer organizations responsible for 106 million lives across the U.S., conducted by Dobrovolny’s Advance Insights unit between February 2008 and March 2009, sheds some light on how payors are currently managing orphan drugs and suggests the way it is likely to evolve in the future. According to the findings, the patient share of orphan drug costs has been on the rise, and “this shift in design benefit could affect patient access to orphan agents, and therefore, impact drug utilization,” she says. Perhaps not surprisingly, the survey found that clinical data associated with the orphan drug ranked highest among the factors that drive benefit design or restrictions in most plans, followed closely by overall cost exposure by the payor.

Meanwhile, as a result of new healthcare-reform efforts, the specter of increased control that might be exerted if the government becomes the predominant payor in the market could have a chilling effect on investment in biotech entities. “The biggest risk to the Orphan Drug Act is the potential for fixed government pricing,” says D2 Pharma’s Erhardt. “Investments will continue to go where they can be rewarded.”

Again, the high-touch role that specialty pharmacy distributors bring to the orphan drug arena puts them in the ideal place to provide the services and gather the data needed to demonstrate better health economic outcomes. Xcenda recently completed a survey of with 50 managed-care decisionmakers whose companies represent more than 150 million covered lives. The study found that 86% of payors believe that fewer than 20% of the new products
There are orphan diseases (defined as patient populations under 200,000) and then there are “ultra-orphan” diseases, which Centric Health Resources (Chesterfield, MO), among others, defines as under 20,000. The company’s third annual conference, which it underwrites for attendees, brought together manufacturers, healthcare providers, patient advocates and industry analysts to explore this evolving area of healthcare. A keynote address was made by Andrew Von Eschenbach, MD, former FDA Commissioner and now affiliated with The Center for Health Transformation (Washington, DC).

A theme running through several of the presentations was that, even though care of patients with orphan or ultra-orphan diseases is some of the most expensive drug-based therapy in existence (with costs ranging upwards of $400,000 annually, according to MME, one of the presenting companies), insurers and healthcare systems are prepared to handle these patients (with a generous assist from manufacturers and patient-care organizations), although linking sources of reimbursement with patients is a constant source of struggle. And, at these stratospheric price levels, quality of care becomes a defining characteristic—in general patients who successfully stay on therapy have lower overall healthcare costs than those who do not (which is an activity Centric stakes its manufacturer services on). Unlike other therapeutic areas, however, patients themselves are often the key opinion leaders, having more knowledge than the average physician about their disorders, and being networked to other patients where user experiences are shared.

Von Eschenbach reiterated a theme well known from his days as FDA Commissioner: The scientific breakthroughs in pharmacogenomics presage a new era of personalized medicines and therapies. With more science—and with a willingness to fund treatment—the industry can expect a growing market in ultra-orphan therapies.

The next Centric Conference is scheduled for Sept. 19-21, 2011.

To help their case, drugmakers “should consider investing in budget-impact models, comprehensive managed-markets-awareness campaigns, and risk-sharing contracts in order to develop a more-compelling picture of their products and optimize the overall patient access and reimbursement situation,” says Grogg of Xcenda.

**Personalized medicine**

Ongoing research in the orphan drug arena is widely expected to benefit from the increased use of personalized-medicine approaches to diagnosis and treatment that will arise from ongoing promising breakthroughs in biotechnology and genomics research.

Researchers have now defined the genetic basis of more than 2,000 rare diseases and this is helping the research community to improve orphan drug development for many rare and neglected diseases. Down the road, testing protocols based on “personalized medicine testing could make a critical difference in making sure that the right medication is given to the right patient, and that expensive drugs are used by individuals who will obtain clinical benefits,” says Russek of Accredo Health Group. Such advances will help researchers to look at individual patients and see if the body will respond to a given drug based on some measurable biomarker.

With the ability to slice and dice a given cancer based on the genetics of the person or the tumor, drug developers are increasingly able to identify certain cancers caused by a certain gene defect. In this way, “Science is helping us to make small diseases out of big diseases, and that sort of blows up the whole Big Pharma model, doesn’t it?” says Kephart of Centric. “If we ever find that diabetes or heart disease is actually a group of 100,000 rare diseases, that will change everything.”