BioProcess International eBooks

PERSPECTIVES ON ORPHAN-DRUG DEVELOPMENT

Cheryl Scott

By definition, an *orphan disease* affects a small percentage of the population. However, with some 7,000 such conditions identified so far, they collectively have a significant impact on global health. An estimated 350 million people are affected worldwide by a rare disease — altogether more than the population of the world's third largest country (the United States).

International definitions vary: In US parlance, orphan conditions are those that affect <200,000 people; in Europe, a disease is considered rare if it affects <50,000 people. And a condition can be considered rare in one part of the world but common in another. Most rare diseases are genetic in origin. Half the affected patients are children, and half the conditions have no devoted research foundations.

Some well-known biopharmaceutical companies are devoted to innovating in the rare-disease segment: e.g., Alexion, BioMarin, Celgene (a subsidiary of Bristol Myers Squibb), Genzyme (part of Sanofi), Isis, Onyx (Amgen), Shire (Takeda), and Vertex. But the vast majority of orphan conditions have no treatments approved by the US Food and Drug Administration (FDA). During the first 25 years of the Orphan Drug Act (passed in 1983), 326 such drugs were approved for the US market. Just 350 are most prevalent of the 7,000 orphan diseases — affecting 80% of rare-disease patients — and thus the most likely candidates for pharmaceutical intervention. And many people either have or know someone with a rare disease.

While introducing our niche-disease spotlight series back in 2015, I discussed the practicalities of orphan-drug development with BPI editorial advisor Jim Faulkner (venture partner at Apple Tree Partners in London, UK; chief technology officer at Ascidian Therapeutics in Boston, MA), who was at the time vice president of rare-disease manufacturing and supply at GlaxoSmithKline (GSK). "Criteria that lead us to progress a candidate into development include high unmet medical need; clearly defined disease etiology and mechanism of action; significant

probability that a target can be treated with available technologies; and an ability to synergize development costs with (or 'repurpose' candidates that have failed for) other indications."

I wondered why rare-disease programs seemed to be the purview of smaller companies. "Many facets of rare-disease drug development do not fit easily with the historical 'big pharma' model of industrial scale and mass marketing," Faulkner explained, "such as a potentially small customer base, specialized supply chains, and nonstandard development pathways. So the history of drug development in rare diseases has been dominated by smaller, more specialized 'niche' biotech companies. Fortunately, a number of developments have made the case for investing in a specialized rare disease venture much more persuasive."

Chief among those, he noted, is increased scientific and genetic understanding of rare-disease etiology. The regulatory environment has evolved to include global orphan drug policies and FDA initiatives such as breakthrough-therapy designation and priority-review vouchers. "Commercially," he added, "orphan drugs are characterized by enhanced exclusivity protection, lower marketing costs, faster uptake, and appropriate pricing."

So "big-pharma" companies have made serious entry into the rare-disease space — illustrated by the list of smaller companies above, many of which are now subsidiaries of larger organizations. GSK set up its own dedicated team in 2010 to "look for creative solutions to deliver potential medicines to patients — whether through our own internal R&D engine, licensing opportunities, collaborative partnerships, or focused investments."

With smaller potential markets, chemistry, manufacturing, and controls (CMC) programs in developing orphan drugs face even more cost pressure than those devoted to products with larger potential markets. "CMC development of orphan drugs faces a number of particular challenges," Faulkner said. Those include specialized supply chains ("often direct to patient") that necessitate a highly personalized approach. Rapid progression from clinical data to market (often including a compassionate-use program) usually keeps the process used for clinical supply unchanged when a product launches commercially. That necessitates a very integrated approach to research, development, and manufacturing.

Low-volume production of orphan drugs often limits their batch history, Faulkner added, making it difficult to build a significant data set of process operating data. "There is a natural marriage between rare-disease indications and pioneering technologies: cell/gene therapies, antisense oligonucleotides, and therapeutic proteins." But associated manufacturing technologies can be unproven and highly specialized.

"It simply isn't possible," Faulkner explained, "to bear the cost of a full CMC development program of a new technological platform for a very rare disease and still make any kind of return on that investment. Fortunately, regulators recognize that difficulty and are willing to work closely with manufacturers to tailor a CMC registration package that's 'fit for purpose' in a disease with high unmet need — without compromising product quality."

And competition is an increasing concern. What if more than one company targets a given condition? "We do increasingly see competition in a few specialized, established rare-disease areas," said Faulkner, "such as lysosomal storage disorders." But orphan-drug designation establishes a period of exclusivity for companies that are first to market with a particular treatment modality for a specific indication. "The only way that following companies can break that exclusivity period is if their new treatments are significantly different and offer a superior clinical benefit," he said. So if a company initiates a new development program for a condition

that already has a treatment, it needs a clear reason to believe that the new drug really will be better for patients.

Other countries have their own legal provisions that, like the US Orphan Drug Act, incentivize drug development for rare diseases. A 2018 article compiles information on those for 23 countries. International Rare Disease Day takes place on the last day of February every year, with an objective of raising awareness among the general public as well as policy-makers, public authorities, industry representatives, researchers, and health professionals. Informa Connect's Biotech Week Boston — which hosts the annual BPI Conference and Exhibition — has partnered with Rare Disease Day's annual film festival in Boston, MA, since its inception in 2017. You can find information about upcoming events and associated partner organizations online at www.rarediseaseday.org.

Three Dimensions of Drug Development for Rare Diseases

Martine Zimmermann is senior vice president and global head of regulatory affairs for Alexion Pharmaceuticals in Zürich, Switzerland. She has 25 years of experience in drug development and regulatory affairs with both classical drugs and biologics/vaccines for markets in the United States, Europe, Japan, and the rest of the world. Zimmermann holds a doctorate in pharmacy from the Université Louis Pasteur (Strasbourg, France), and she worked with Servier, Aventis, and Rhône Mérieux/Merial before joining Alexion. She serves on the boards of directors for both Inventiva Pharma and Caelum Biosciences.

Tania Pereira Chilima is chief technology officer for Univercells Technologies (Nivelles, Belgium), where she focuses on driving innovation of breakthrough viral-vector technologies for gene therapies and vaccines. Previously, she worked as a postdoctoral researcher (sponsored by the Bill and Melinda Gates Foundation) with Pall Corporation and University College London, from which she holds an engineering doctorate.

Monica Weldon is founder, president, and chief executive officer (CEO) of Bridge the Gap — SYNGAP Education and Research Foundation. In November 2012, her son Beckett was diagnosed at Texas Children's Genetics Clinic with the gene mutation SYNGAP1. She started to blog about his progress, which built a community of parents and caregivers that has become a strong support group. After 23 years teaching science in secondary education, she retired to focus on building the programs and promoting the mission of her organization. She is primary investigator on the SYNGAP1 (MRD5) Registry and Natural History Study and a consultant on rare-disease business strategies, advocating for rare-disease legislation at state and federal levels.

This past spring, I got together with each of these women to talk about the risks and rewards of drug development for rare diseases. Brought together into this virtual roundtable, the resulting discussions provide a three-dimensional picture of the challenges and benefits of this endeavor from the perspective of patients, drug developers, and technology providers. . .

Find the full interview in our special eBook on development of treatments for rare diseases at the link below. Also included is an article on patient support for rare-disease clinical trials by Clincierge CEO Scott Gray.