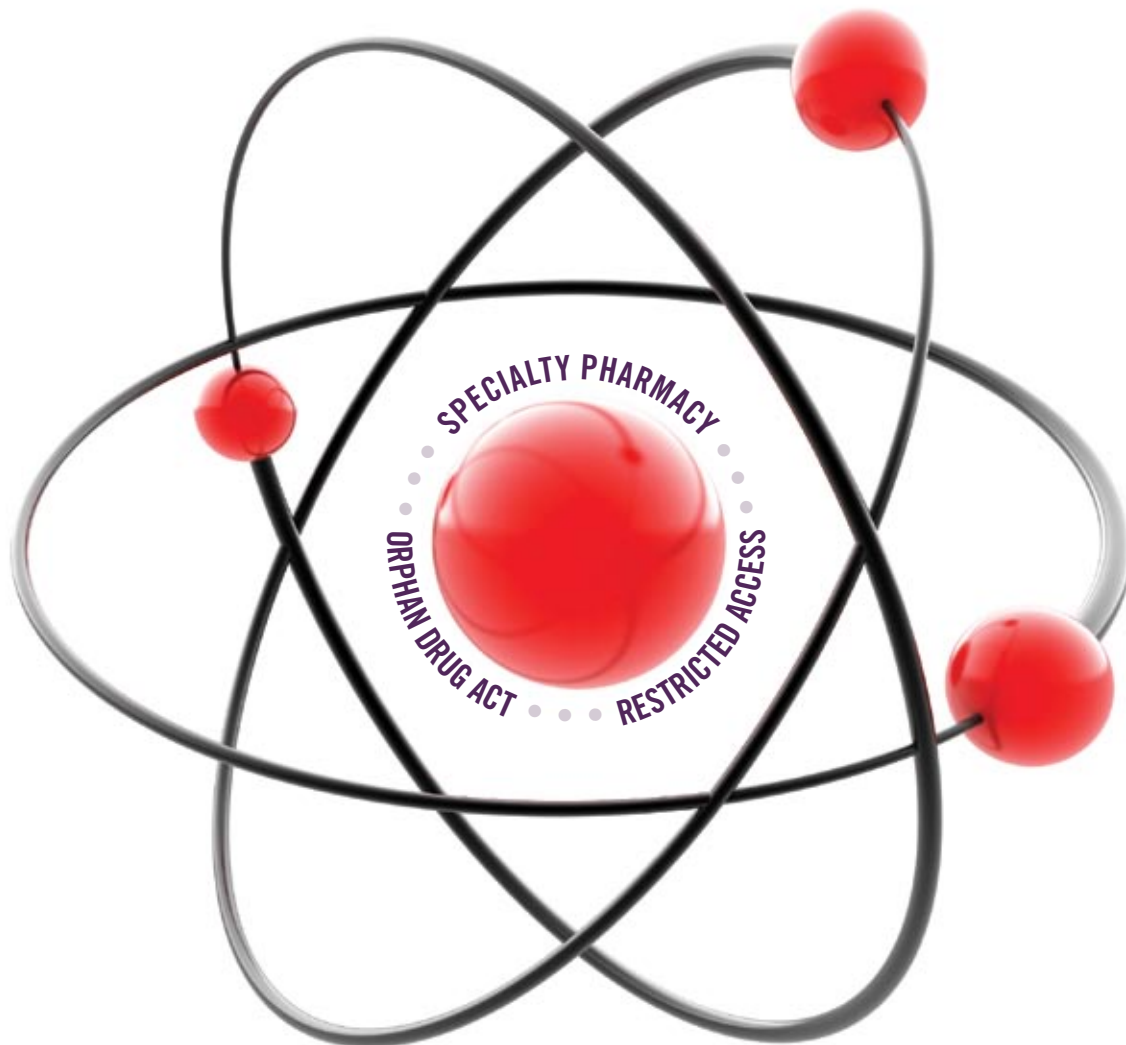




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Celebrating 25 Years of the Orphan Drug Act

By John Watson

A boon to patients and biotech alike, the Orphan Drug Act has stimulated the development of several of the biggest blockbuster drugs in oncology.

Despite the best efforts of determined researchers, drug development almost always occurs through incremental advances rather than monumental breakthroughs. Research begets more research and, if we're lucky, a new treatment emerges years down the line. While this paradigm still holds true today, there is an occasional watershed moment that forever alters the landscape of contemporary treatment.

One such moment occurred 25 years ago, not in a research lab but in another environment not traditionally associated with rapid innovation—Washington, D.C.—when President Ronald Reagan signed the U.S. Orphan Drug Act (ODA) into law on January 4, 1983. As a result of this legislation, previously neglected patients saw their treatment prospects improve seemingly overnight and the modern biotechnology industry as we know it was born.

Measuring the Impact of the ODA

“It's probably not an exaggeration to say that there's no other piece of legislation that's had such a profound impact on patients, caregivers, biotechnology, and venture capitalists as the Orphan Drug Act,” said James C. Greenwood, president and CEO of the Biotechnology Industry Organization. “It's been absolutely critical to the establishment of a series of new companies, such as Amgen, Genzyme, Biogen Idec, and countless others.”

An estimated 25 million Americans are believed to suffer with one of the approximately 7,000 so-called “orphan diseases,” defined by the ODA as diseases affecting less than 200,000 citizens. While individually these ailments are rare, collectively they occur in more than 1 out of 10 people in the United States. In years prior, patients with orphan diseases faced a stark reality of lim-



ited treatment options and correspondingly poor long-term prognoses, as pharmaceutical companies were wary of making the considerable financial investments required to bring a drug to market that would have only a limited patient base.

“Companies were developing drugs for only the most prevalent conditions, such as hypertension and arthritis, and simply wouldn’t bother with the development of drugs for rare diseases,” said Abbey Meyers, founder and president of the National Organization for Rare Disorders (NORD).

Through the tireless work of NORD—at that time an informal coalition of rare disease support groups—and other interested parties, the ODA was passed in Congress in 1982 and written into law the following year. The ODA sought to stimulate the development of orphan treatments by offering a series of incentives to companies, including New Drug Application fee waivers, tax credits and grant funding for clinical research, and marketing exclusivity for orphan products.

“By enhancing the incentives, it had a magical effect on the industry and created this huge growth in the development of drugs for orphan indications,” said Greenwood.

“In the decade prior to 1983, we developed only 10 new drugs for rare diseases. Since then we’ve seen about 11 new drugs a year, with 1,749 having entered the research pipeline and more than 300 of those eventually receiving market approval.”

Orphan Drugs for Cancer

Nowhere has the upsurge in drug development been as dramatic as in the treatment of rare forms of cancer.

“Something close to 40% of all orphan drugs have been for rare cancers,” explained Meyers, who cited Celgene’s development of Thalomid® (thalidomide) as emblematic of the ODA’s effect in oncology. Despite early signs of promise, Thalomid was roundly ignored by major pharmaceutical companies given its potentially minor market share and negative connotations stemming from its highly publicized role in causing severe birth defects in children in the late 1950s/early 1960s. However, Celgene was able to successfully repurpose the drug under the banner of the ODA for the treatment of multiple myeloma (as well as an earlier indication for erythema nodosum leprosum). Though Thalomid is trending slightly downwards, due primarily to competition with Celgene’s own second-gen-

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eration thalidomide derivative Revlimid® (lenalidomide), itself a beneficiary of orphan drug status, it still managed to post \$447.1 million in net product sales in 2007. For its part, Revlimid's global sales are expected increase 60% in 2008 to roughly \$1.25 billion.

Thalomid is just one of several agents to significantly impact the treatment of myeloma as a result of the ODA, according to Susie Novis, co-founder and president of the International Myeloma Foundation.

“Every major drug currently used to treat myeloma began life as an orphan drug. Thalomid, Velcade, Revlimid, Aredia, and Zometa all had orphan drug status prior to FDA approval. These novel drugs owe their existence to the Orphan Drug Act,” she said. “Without orphan drugs, the last five years’ advances in myeloma treatment simply could not have been made. These novel drugs have become the mainstay of current treatment strategies, and as a result we’re seeing increased survival, prolonged remissions, and better quality of life for patients with myeloma.”

Development of orphan drugs for rare cancers continued at a remarkable pace in 2007. New agents receiving market approval in 2007 include Doxil® [doxorubicin HCL liposome injection; Ortho Biotech] in combination with Velcade® [bortezomib; Millenium, Johnson & Johnson] for multiple myeloma; and Torisel™ [temsirolimus; Wyeth] for the treatment of renal cell carcinoma. Among the 80 products listed as receiving orphan designations in 2007, more than 30 were for indications in rare cancer, although only the coming years will tell whether any of these agents make good on their promise or if they will join the countless others that failed to pass late-stage clinical testing.

A Boon to Biotech

Had the ODA remained as it was originally signed into law, it is highly doubtful it would have had the impact it did. Only through a pivotal amendment two years later did it transform into the tremendous catalyst for biotech growth we know today.

“In 1985, the Orphan Drug Act was amended because it only covered chemical drugs, so at that point biologics were added as well,” said Meyers. “It really took off from there, because at that stage the biotechs were really in their infancy. Patent laws weren’t strong enough for a lot of the biological drugs and they looked at the Orphan Drug Act as a much better way to guarantee they could bring their agents to market.”

Among the beneficiaries of this amendment are current titans of the biotechnology industry Genentech, Amgen, and Genzyme, whose first products to receive marketing approval were originally developed as orphan drugs.

Perhaps the biggest incentive encouraging biotechs to set their sights on orphan indications is the ODA’s favorable exclusivity clause, which states that no other company can receive marketing approval for an identical agent in the same indication until seven years after the date of marketing approval is granted to the first agent, unless the new agent is proven superior.

However, some believe that the ODA’s incentives do not actually encourage companies to develop treatments solely with an orphan indication in mind so much as they provide them with a convenient launching pad with which to later expand into larger, more financially beneficial indications.

“It’s so risky and difficult to develop a cancer drug that if you have to just develop it on its own merit, you wouldn’t set out as a company for a very niche group,” said David R. Parkinson, MD, who previously served in senior drug development roles at Biogen Idec, Amgen, and Novartis before becoming president and CEO of the biotechnology company Nodality, Inc. in 2007. “In cancer drug development, you may begin by looking at the drug in a small subset of patients, but you have to expect that eventually the biology will go into other areas, because from a corporate point of view you could not justify building a company or putting the resources into only a small application.”



This is the story of Gleevec® (imatinib mesylate), which Parkinson had a key role in bringing to market during his tenure at Novartis. Gleevec originally obtained an orphan indication for the treatment of chronic myeloid leukemia, but eventually went on to receive six additional orphan indications on the way to becoming a certified blockbuster with just over \$3 billion in sales in 2007. Thalomid would appear to be seeking a similar path and is currently under investigation for a variety of broad oncological indications, including malignancies of the prostate, pancreas, and colon.

Parkinson conceded that obtaining multiple indications may be a more pressing concern for established pharmaceutical companies than it is for up-and-coming companies, and added that obtaining an orphan indication could mean a lot to a fledgling biotech simply in terms of attracting investors.

The Future of the ODA

Although few would argue against the impact of the ODA, what has been a topic of controversy are the high costs associated with many of these treatments, such as Erbitux® [cetuximab; ImClone, BMS, Merck], Revlimid (lenalidomide, Celgene), and Sprycel® [dasatinib; BMS].

With pressure mounting from both patient groups and payers to reign in costs, some have proposed setting limitations on the profits that can be made from orphan drugs. In Meyers' perspective, this would be an unnecessary tactic that could have potentially detrimental effects on future development.

“If a company develops a drug for rare diseases, they have to charge more because the number of patients taking it is going to be fewer,” she said. “Yes, these costs are a problem, but what we tell companies is that there are a lot of people out there with no health insurance or inadequate health insurance, so you have to develop a medication assistance program. Consequently, all of these companies have those programs now.”

She added that NORD is more concerned with helping the FDA obtain the resources they need to effectively do their job and with protecting the ODA from the political maneuvering of members of Congress that would weaken it by favoring one drug or company over the others.

A more subtle challenge to the ODA is perhaps found in the drive to provide individual subtyping for a wide variety of cancers. Parkinson's company Nodality, Inc. is one of several emerging biotechs invested in the design and testing of patient-specific disease classification technology that will potentially divvy up diseases into even smaller subtypes.

“Underlying the broad, classic disease categories that we are taught to think in is much more inter-patient variability,” Parkinson said. “For treatment to become more efficient, patients will need to be characterized individually and treated accordingly.”

Whether the term “orphan disease” will even be relevant in a world of such individualized diagnoses will be just one question facing the ODA in its next 25 years. **JW**