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Hopes, Fears for Orphan Drug Act

Passed 40 years ago, it may be time for ODA 2.0

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As the Orphan Drug Act slides into middle age, patient advocates and biopharma companies are applauding its accomplishments, lamenting legislative setbacks that have limited its utility, and developing proposals for expanding its reach.

In the 40 years since the ODA was signed into law, FDA has approved more than 600 drugs for orphan conditions, up from 10 in the prior decade. The success has been tangible, but new policies will be needed to increase the pace of drug development if society is to come close to meeting the needs of the millions of patients living with thousands of rare conditions that have no treatments.

The ODA has been successful because it aligns the financial interests of drug companies with the needs of patients. It has been controversial from its conception because it is based on the notion that the best way to help people suffering from rare diseases is to make it profitable — and in some cases very profitable — to create drugs for small populations.

Celebrations of the ODA's anniversary are muted because that controversy has led to laws that have rolled back incentives for orphan drug development. Members of Congress from both parties, along with academic critics, point to blockbuster orphan products as support for their contention that the ODA is an unnecessary form of corporate welfare.

Those voices prevailed in 2017 when Republicans halved the orphan drug tax credit to 25% after first proposing to scrap it or limit it to a single indication.

"We're incredibly tired of the erosion of the ODA."
Annie Kennedy, EveryLife Foundation

Skepticism about the need to incentivize orphan drug development surfaced again last year.

Democrats included a provision in the Inflation Reduction Act (IRA) that exempts an orphan drug from Medicare price-setting if it has been approved for one — and only one — indication. Biopharma companies say the single-orphan exemption is already altering the course of drug development, leading them to abandon second indications.

The ODA was created by patient advocates. A new generation of advocates is trying to restore incentives, and to find new policies that are attuned to scientific and economic circumstances that have changed immensely since 1983.

"We're incredibly tired of the erosion of the ODA," Annie Kennedy, chief of policy, advocacy & patient engagement at the EveryLife Foundation for Rare Diseases, told BioCentury. "We're grateful for the progress that's come since the passage of that landmark legislation, but 40 years later, I think it's really time that we start to think about how we expand on that great work."

Some rare disease advocates are calling for Congress to enact ODA 2.0 to catalyze the creation of therapies for the 90% of orphan diseases that have no FDA-approved treatments. Ideas include tiered incentives that are larger for the smallest patient populations, such as higher tax credits for ultra-rare disease drug development than for less rare indications, establishing a rare disease center of excellence at FDA, and creating explicit instructions on when and how FDA should exercise regulatory flexibility.

Optimism is hard to come by in Washington this year, but there are signs that the quest for better medicines can breach the partisan divide.

Even as it has chipped away at the ODA, Congress has continued to promote biomedical progress, including for rare conditions. In 2022, it created and provided $2.5 billion to the Advanced Research Projects Agency for Health (ARPA-H) and created new approval pathways for platform technologies and the review of drug manufacturing platforms that could lead to more — and less expensive — treatments for rare diseases. The omnibus budget bill also included requirements for FDA to study the ways Europe regulates drugs for rare diseases and consider whether it should adopt practices from the other side of the pond.

Other initiatives that signal commitments to patients with rare diseases include the Bespoke Gene Therapy Consortium, a public-private partnership that is developing new approaches to gene therapies for ultra-rare diseases, and the n-lorem foundation, which is creating and providing experimental treatment for the rarest of rare diseases and providing them to patients at no cost.

The power of an idea

The Orphan Drug Act and laws it inspired are testaments to the power of an idea, the force of patient advocates, and the effectiveness of financial incentives.

The idea to organize science and regulations around rare conditions, and the related notion that low-prevalence diseases are neither unimportant nor uncommon, seem obvious now but were novel four decades ago.

Three decades later, Nancy Goodman, grieving the death of her son from medulloblastoma, persuaded Congress to enact the Creating Hope Act, a bill that created priority review vouchers (PRVs) for rare pediatric diseases.

The ODA had many champions. The driving force was a mother, Abby Myers, who was outraged by the fact that drug companies would not invest in R&D to find treatments for her son and other children suffering from rare diseases.

While industry came to strongly endorse the ODA and pediatric PRVs, biopharma trade associations opposed both the ODA and Creation Hope Act when they were introduced.

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Heidi Ross, National Organization for Rare Diseases

Originally applicable only to unprofitable products, the ODA was expanded over time into a launch pad for commercially successful products. It grants seven years of exclusivity to drugs for diseases that affect 200,000 or fewer Americans, provides tax credits for R&D needed to create orphan drugs, and waives user fees for orphan drugs.

"Ronald Reagan's words the day he signed the bill into law on January 5, 1983 still have meaning today," John Crowley, executive chairman of Amicus Therapeutics Inc. (NASDAQ:FOLD), told BioCentury. Reagan said: "I only wish that with the stroke of this pen I could also decree that the pain and heartache of people who suffer from these diseases would cease." They didn't end with the stroke of his pen, Crowley noted, "but the ODA did create a sustained environment and market-based system of incentives that have advanced rare disease research and led to hundreds of new treatments that likely never would have otherwise happened."

The economic incentives created by the ODA were important to Amicus. The company, founded in 2002, markets orphan drug Galafold migalastat, has another orphan drug in registration and three iin earlier stages of development. "The tax credit, the seven years of orphan exclusivity, and even the waiver of PDUFA fees are all valuable tools that helped sustain Amicus' development until we launched Galafold for Fabry disease," Crowley said. "These continue to support our growth today, where we have a second medicine, for Pompe disease, that is being reviewed by the FDA."

For Amicus, the seven years of market exclusivity is the most powerful incentive in the ODA, Crowley said. "It sets a floor for protecting innovation and enables us to use a range of molecules, tools and technologies that may otherwise not be utilized as we search for treatments for these diseases."

Slashing the tax credit

The orphan drug tax credit has also been important for Amicus and other companies, Crowley said, because it "helps to offset the very large sunk costs involved in running clinical trials, which is especially challenging for rare diseases."

The reduction in the value of the orphan tax credit "has to have had an impact," Crowley told BioCentury. "For companies working in this space, or for larger companies who are considering purchasing smaller biotech companies who might have an orphan product in development, those credits can offset present or future tax liabilities. Reducing those incentives reduces the net present value of these programs."

Crowley added: "At the margins, reducing the credit has an impact on investors who have many investment vehicles to choose from — from large pharma to commercial real estate. The math can change those investment choices."

Patient advocates fought the cut.

The National Organization for Rare Diseases was "disheartened when the orphan drug tax credit was reduced to 25% in 2017," Heidi Ross, NORD's VP for policy and regulatory affairs, told BioCentury. "We don't know the impact on orphan drug development because it takes so long to develop drugs. NORD is strongly advocating for the tax credit to be increased to 50%, and we have fought ferociously against subsequent efforts to further reduce the credit."

The Rare Disease Company Coalition (RDCC), an advocacy group that represents companies that develop orphan drugs, is also lobbying to restore the tax credit to its previous level. The coalition has 22 members.

"We hear from the majority of our member companies that the orphan drug tax credit is one of the most important, if not the most important incentive" for developing drugs for rare conditions, RDCC Executive Director Amanda Malakoff told BioCentury.

A study conducted by Ernst & Young for BIO and NORD found that if the orphan drug tax credit had not been available, one third of the orphan drugs approved in 1995-2015 would not have been developed, and that eliminating the credit would cut future development by a third. The study did not estimate the impact of halving the credit.

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The EveryLife Foundation wants Congress to restore incentives, but has not determined what action it will seek on tax credits, Kennedy said.

Some advocates are calling for future incentives to focus on ultra-rare diseases, but others are cautious about taking steps that could alienate some of their stakeholders or lead to reductions in incentives for creating medicines for people with diseases at the upper end of the orphan spectrum.

"We think there needs to be a scientific approach to thinking about whether and how we define ultra-rare," Kennedy said.

NORD opposes making distinctions for incentives based on disease prevalence, Ross said.

Jim Geraghty, author of *Inside the Orphan Drug Revolution*, however, thinks it makes sense to focus on ultra-orphan conditions, which he defines as affecting 10,000 or fewer Americans.

"If as an industry we need to have negotiation and some give-and-take, I would say we should be willing to accept cuts to the credit for more prevalent diseases in exchange for getting a greater tax credit on ultra-orphan drugs," said Geraghty, who serves as chairman of three biotechs, Orchard Therapeutics plc (NASDAQ:ORTX), Pieris Pharmaceuticals Inc. (NASDAQ:PIRS) and Idera Pharmaceuticals Inc. "I wouldn't mind giving up the tax credit for diseases with a prevalence of 150,000–200,000 patients, a market size that many biotech companies see as sustainable, in exchange for a 100% tax credit on the ultra-orphan diseases."

Orphan drug tax credits can be "absolutely critical" for helping small companies invest in the development of drugs for rare indications, Steven Pfanstiel, CFO of Marinus Pharmaceuticals Inc. (NASDAQ:MRNS), told BioCentury. Reducing the size of the credit is "absolutely going to constrain" the number of indications Marinus can study, he said.

Pfanstiel added, however, that tax credits are only useful to companies that are profitable. Marinus' first drug, Ztalmy ganaxolone, was approved in March 2022 to treat seizures associated with CDKL5 deficiency disorder, a rare genetic epilepsy, in patients two years of age and older. The company is targeting the pediatric population, about 2,000 patients in the U.S.

"Having just launched, we have very limited revenues at this point" and hence no ability to take advantage of tax credits, Pfanstiel said.

Rare pediatric PRVs

Two other incentives, rare pediatric priority review vouchers and the user fee waiver, have been critical for development of Ztalmy, he added.

Marinus sold a voucher it had received for Ztalmy for $110 million in July 2022. "The priority review voucher was huge," Pfanstiel said. "It provided a significant amount of funding runway that was critical."

From its inception in 2012, the value of the pediatric PRV program has been limited by sunset clauses. Under current law, FDA cannot award any vouchers after Sept. 30, 2026, so companies starting development today cannot be certain that the vouchers will be available when their drug is ready for FDA review.

The RDCC is lobbying to have the program made permanent.

It is also asking Congress to provide an incentive to companies to complete clinical trials that were stopped or delayed because of COVID-19 restrictions and lockdowns. Malakoff said, "That had an outsized impact on patients with rare diseases who were at a higher risk."

The RDCC is seeking a six-month extension on the seven-year orphan exclusivity for drugs approvals supported by trials that were interrupted by the pandemic.

Single-orphan exemption

The single orphan exemption in the IRA has led one company, Alnylam Pharmaceuticals Inc. (NASDAQ:ALNY), to announce that it has put on hold plans to study a second indication for an approved orphan drug.

An analysis by BioCentury identified 18 other drugs from 17 other manufacturers that were approved for a single orphan indication in 2021 or 2022 and are being studied in clinical trials for at least one additional indication.

By creating the single-orphan exemption, Congress has asked "researchers to close their eyes to potential new treatments for rare disease patients," Crowley said. "It's maddening."

RDCC's Malakoff noted that the "science behind rare diseases supports an already approved drug being repurposed for use in another rare condition."

The RDCC wants Congress to expand the exemption to cover all orphan drugs, regardless of the number of indications on their labels.

Getting any legislation passed in the 118th Congress will be extraordinarily difficult. Changing the IRA's singe-orphan exemption is especially problematic because Democrats do not want to revisit the law, and members of both parties are reluctant to take any action that appears to benefit pharmaceutical companies.

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There are differing views on the topic within the pharmaceutical industry, with some companies that do not market orphan drugs opposing efforts to expand the exemption, Washington representatives of PhRMA members told BioCentury.

NORD is trying to leverage ambiguities in the IRA to convince CMS to implement the law in ways that would reduce disincentives to developing additional indications for orphan drugs. "We believe there is a need to clarify how it will be implemented," Ross told BioCentury. It is unclear, she said, if the timeline for when a product becomes negotiation eligible — seven years for drugs approved under NDAs and eleven years for BLAs — "starts from the first approval or the second approval."

If NORD persuades CMS to start the clock ticking after a second orphan indication is approved, companies could gain up to an additional nine to 13 years to market their drugs before the IRA's price-setting provisions kick in.

NORD is also working to protect the exemptions of orphan drugs that have more than one indication for the same orphan disease. "We would like HHS to be explicit in how they are going to treat a product with multiple indications for the same disease," Ross said. "We would like to see a product with a designation and with multiple approved indications for the same designation remain exempt. For example, a product to treat cystic fibrosis may have multiple approved indications to treat different populations with cystic fibrosis. We want to clarify that, in this situation, that product it is exempt from negotiations" if all the approved indications are for CF.

Clarifying flexibility

Rare disease advocates are also focused on applying regulatory innovation to support the development of more medicines for orphan diseases.

The agency's approval of Relyvrio from Amylyx Pharmaceuticals Inc. (NASDAQ:AMLX) for amyotrophic lateral sclerosis (ALS) serves both as a template for future orphan drug approvals and as an indicator of the need for greater clarity about the agency's approval standards, Frank Sasinowski, chair of the EveryLife Foundation's board of directors and a director at Hyman, Phelps & McNamara, told BioCentury.

In September, Sasinowski, who represented Amylyx, highlighted FDA's explicit reliance on "regulatory flexibility" and its comparison of the evidence supporting Relyvrio to the evidence that supported other drugs approved for ALS. He also noted the agency's explicit acknowledgement that patients with serious diseases who have no good options are willing to accept greater uncertainty about a drug's benefits compared with patients who have more options or less dire circumstances.

There is an urgent need for Congress or FDA to provide FDA reviewers, the public and drug developers with guidance about the use of the flexibilities that underpinned approval of Relyvrio and many other orphan drugs, Sasinowski told BioCentury last week.

He compared the situation to "coloring outside the lines."

Reviewers of orphan drugs, Sasinowski said, are told "you have a requirement to color outside the lines, but we're not going to tell you what colors you can use, and we're not going to tell you how far you can go outside the line before you've gone too far."

While FDA could craft guardrails for the application of regulatory flexibility, some changes that would advance orphan drug development would require legislation.

If there is an ODA 2.0, it could include provisions allowing FDA to approve medicines for ultra-rare conditions using parameters similar to those in the emergency use authorizations that were used to speed deployment of COVID countermeasures.

"That would be a reason for ODA 2.0, because essentially Congress would be declaring a national emergency because there are 10,000 rare diseases, most of them under 3,000 people in the United States, and 95% of these diseases do not have any FDA approved therapy," Sasinowski said. "It is a real emergency for these people."

It isn't necessary, and in many cases it may be impossible, "to generate the same level, same quantum of or certainty in the of evidence of efficacy for ultra-rare diseases as for more common diseases," he said, adding that for diseases that affect only a handful of people, "tools like randomized-controlled trials, which are the 'gold standard' for common diseases, can even can produce misleading data in ultra-rare conditions where not all prognostic features are known."

If Congress can be convinced to pass an ODA 2.0, the orphan diseases advocacy community is likely to reiterate its calls for the establishment of a center of excellence for rare diseases. FDA has resisted the idea, advocates contend it is needed to provide the expertise, the consistency across divisions and centers, and the resources that are critical for effective oversight of orphan drugs.

Legislation could also help reduce the burden of the diagnostic odyssey that bedevils most patients with rare diseases. Increased government investment in genomic screening, especially for newborns, and incentives for improved diagnostics, would make it possible to identify and, in many cases, treat rare diseases years or decades sooner than typically happens today.