The study by Monge et al\(^1\) was written by senior officials at the US Food and Drug Administration (FDA) and provides a detailed overview of novel drug approvals and the use of expedited pathways over almost 2 decades. In their analysis, they identified 581 novel drugs that were approved between 2008 and 2021. Of these drugs, 252 (43.4\%) were approved as orphan drugs, and many were approved using expedited pathways.

The Prescription Drug User Fees Act (PDUFA) stipulates the funding mechanism for the FDA and specifies drug approval priorities. Its periodic reauthorization represents an opportunity for the FDA and Congress to consider potential solutions to policy issues involving orphan drugs and expedited approval pathways.

The Orphan Drug Act, enacted in 1983, was designed to incentivize drug development for rare diseases. The act provides several financial incentives for drug companies, including a tax benefit to promote drug research and development. Since the enactment of the Orphan Drug Act, the number of novel drug treatments for rare diseases has increased substantially. At the same time, there are concerns that the original intent of the act has been compromised. In 2016, 7 of the top 10 best-selling drugs in the US had an orphan drug designation, including the best-selling drug adalimumab.\(^2\)

Receiving an orphan drug designation provides numerous advantages to the blockbuster drugs; most importantly, the drug obtains an additional 7 years of market exclusivity for each new orphan indication, helping prevent generic competitors from entering the market. Even though the exclusivity is limited to the orphan indication, and in theory, a generic drug could enter the market to treat other conditions that are not the orphan disease, in practice, only a few generic drugs ever enter through this process. Ultimately, this and other strategies result in increased drug spending.\(^3\) A 2017 change in the tax law reduced the tax credit from 50\% to 25\% for orphan drugs, saving US taxpayers an estimated $20 billion over 10 years. This change, however, did not address the ability of companies selling blockbuster drugs to use the orphan drug designation to prevent generic competition. It also could have reduced drug innovation for new drugs treating rare diseases by reducing the tax credit. Eliminating the use of orphan status for blockbuster drugs and restoring the tax benefit for new drugs would help return the Orphan Drug Act to its original intent.\(^3\)

Monge et al\(^1\) also discuss the growing popularity of expedited FDA approval pathways, particularly Accelerated Approval. Expedited pathways are designed to speed the public’s access to innovative medicines. These pathways provide benefits such as faster FDA approval times and greater communication and coordination with the FDA. In addition, in the case of Accelerated Approval, drugs can be granted market approval using a surrogate marker instead of a clinical end point as a trial outcome. However, there are problems with the use of surrogates; for some surrogates, there is weak correlation with clinical outcomes, and other surrogates may not get validated against clinical end points for several years even as the drug is already being marketed. The recent use of surrogates to obtain approval for aducanumab to treat Alzheimer disease is an example of where the use of a surrogate was controversial.\(^4\)

The time from accelerated approval to full approval can take many years, and drugs are allowed to remain on the market throughout this period.\(^5\) There is little financial incentive for drug manufacturers to complete the confirmatory trial and obtain full marketing approval for their drug because the drug can be commercialized with or without full marketing approval. In addition, it may be difficult to get patients to participate in a clinical trial for a drug that has received accelerated approval, because in the clinical trial, patients might receive the placebo instead of the drug when the
drug is already available in the market. This becomes problematic for payers such as Medicare, which ends up paying for drugs that do not have confirmed benefits and represent additional cost without corresponding benefit if the confirmatory trials fail. It can also harm the patient if the drug is ultimately found to provide no clinical benefit and an alternative treatment could have been used instead.

The article by Monge et al.\(^1\) demonstrates the popularity of the orphan drug pathway and the use of expedited approvals. The reauthorization of PDUFA should include provisions to prevent blockbuster drugs from benefitting from orphan drug incentives as well as provisions to incentivize manufacturers to complete confirmatory trials for drugs with accelerated approval. Such provisions would represent needed incremental change to realign incentives to the original intent of the orphan drug and the Accelerated Approval pathway.

**REFERENCES**


