Preapproval Promises to Voluntarily Withdraw FDA-Approved Drugs

The US Food and Drug Administration (FDA) faces a persistent tension between confidence and speed. The more stringent its gatekeeping requirements for drug approval, the better the evidence for treatment and coverage decisions, but the longer patients wait for products that may help. With urging from Congress, regulated industry, and patients, the FDA has increasingly prioritized speed, opening the gate based on less certain evidence often assuming that it can later be closed.

As difficulties with that assumption have become clearer, there have been calls for firmer approaches to both approval and withdrawal. The FDA's recent approval of Amylyx's Relyvrio (sodium phenylbutyrate and taurursodiol) for the treatment of amyotrophic lateral sclerosis demonstrates the agency's willingness to rely on companies to close the gate on themselves. If the FDA plans to consider company pledges to voluntarily withdraw their products from the market when deciding whether to grant approval, the strength of those pledges must be improved.

Relyvrio's Regulatory Saga

In September 2020, Amylyx published results of its phase 2 CENTAUR trial, which reported statistically significant improvement of the primary end point, i.e., rate of decline (slope) of the total score on the Amyotrophic Lateral Sclerosis Functional Rating Scale-Revised at 24 weeks. Although Amylyx contemplated immediately applying for approval, the FDA sought an additional placebo-controlled trial. Amylyx proceeded with its phase 3 PHOENIX trial, but the FDA later agreed to accept a marketing application before trial completion.

This set the FDA up for a challenge because Relyvrio fell between existing approval paradigms. Although promising, the drug lacked sufficient evidentiary support to generate confidence about granting traditional approval. Yet, Relyvrio had not demonstrated improvement on a surrogate or intermediate clinical end point and was therefore ineligible for accelerated approval, which includes authority for the FDA to require postmarket studies to confirm benefit and to invoke expedited withdrawal procedures in exchange for early market access. Relyvrio also fell outside the other limited categories under which the FDA currently recognizes authority to demand postmarket studies of effectiveness. As a result, the FDA's choices appeared to be either denying approval or granting it in the face of uncertainty with poor postmarket options.

Against the backdrop of strong patient support for approval, the FDA convened an advisory committee in March 2022 to discuss Amylyx's application, which also included data from CENTAUR's open-label extension trial indicating a survival benefit in patients initially randomized to receive Relyvrio. The FDA raised concerns about the CENTAUR trial's statistical analysis, noted that the primary end point result was not "exceptionally persuasive," and questioned the interpretability of the survival benefit. The advisory committee voted 4 to 6, with only a minority agreeing that the data established the effectiveness of Relyvrio.

Amylyx subsequently submitted additional analyses from the CENTAUR trial and its open-label extension, including comparisons with external controls, as well as biomarker data from patients with other neurodegenerative conditions. During a reconvened advisory committee meeting in September 2022, the director of the FDA Office of Neuroscience emphasized the agency's regulatory flexibility alongside continued skepticism regarding whether available data satisfied the "substantial evidence of effectiveness" standard needed for approval. He asked Amylyx if it would commit to voluntarily withdraw Relyvrio should the PHOENIX trial fail to confirm effectiveness. The company responded that if the trial "is not successful," it "will do what is right for patients, which includes voluntarily removing the product from the market." This time, the committee voted 7 to 2 in favor of approval, with some members highlighting the company's pledge. The FDA ultimately approved Relyvrio without reference to the withdrawal commitment.

A Toothless Pledge

Although companies sometimes voluntarily withdraw an approved indication after new evidence demonstrates the drug is unsafe or ineffective, a preapproval pledge to withdraw is unusual, although not unprecedented. When evaluating accelerated approval for drugs with "tenuous" support, the FDA's cancer division has occasionally discussed voluntary withdrawal during advisory committee meetings and asked sponsors to waive their right to a withdrawal hearing in writing before approval, potentially minimizing administrative burdens if companies would be otherwise inclined to force the FDA to overcome barriers present even under expedited withdrawal procedures. Soliciting such a commitment might be an earnest effort to minimize the risks of early approval for promising but uncertain drugs. It could also reflect an illusory promise obscuring the FDA's willingness to lower standards under which companies can profit from unproven drugs.

In either case, it is important to be clear about the nature of Amylyx's pledge. First, it was ambiguous. Amylyx did not define "not successful," leaving room for disagreement. For example, even when primary end points are not met, companies sometimes point to other data, such as promising trends shy of statistical significance, success on secondary end points, or post hoc evidence of benefit. They may also argue that a trial was flawed, necessitating further study. Short of clear findings that the drug...
does not work for any patient—a tall order—Amylyx could claim that it is “right for patients” to keep Relyvrio on the market. Second, Amylyx’s pledge lacked legal effect. Should results of the PHOENIX trial conflict with those of the CENTAUR trial, Amylyx could decide to stop marketing Relyvrio as agreed. If it fails to do so, the FDA could remind Amylyx of its withdrawal commitment, as could the patient community (although previous examples suggest support for withdrawal would likely be mixed). Amylyx might nonetheless refuse, perhaps based on different views of the evidence or new management. In that case, the FDA would be in the same position as if Amylyx had pledged nothing, able to proceed with withdrawal through usual channels available when the FDA’s determination of effectiveness changes based on new information, but without recourse to do more.

Short of an imminent public health hazard, the FDA must notify companies of grounds for proposed withdrawal and afford opportunity for a hearing. An ambiguous statement during an advisory committee meeting not referenced in approval documents, as in the case of Amylyx, would likely not suffice to waive that opportunity. Assuming no new safety concerns, a hearing would focus on whether the effectiveness standard continued to be satisfied, a matter on which Amylyx’s previous statements would be irrelevant. This hearing and withdrawal process can be lengthy (even for accelerated approval drugs), during which time the indication remains approved and sales may continue. It is also important to acknowledge that the FDA may decline to pursue withdrawal given anticipated patient and company resistance, especially in the absence of new treatment options.

Making Company Pledges More Meaningful

Broad reliance on voluntary preapproval withdrawal pledges risks further weakening of FDA approval standards. However, if the FDA plans to seek or rely on such pledges in exceptional cases, such as for drugs like Relyvrio that may offer patient benefit but seem to fall between current approval pathways, we recommend several improvements to strengthen legal obligations and decrease ambiguity.

First, to increase the likelihood of further evidence being produced to inform decisions about continued approval or withdrawal, the FDA should interpret its authority to impose postmarket study requirements broadly; failing that, it should negotiate voluntary postmarket study commitments to resolve open questions. The fact that no efficacy study was included even as a postmarket commitment in Relyvrio’s approval is concerning.

Second, when evaluating a drug for approval, the FDA (and its advisory committees) should only consider withdrawal pledges made in writing, which should be incorporated into approval documents and associated commitments. Moreover, it should include explicit waivers of procedural rights, including the right to a hearing, if the FDA subsequently proposes withdrawal.

Third, triggering conditions for voluntary withdrawal should be clear and specific. Rather than referring broadly to a determination that the trial “is not successful,” as in Amylyx’s pledge, companies could be expected to offer an objective definition, such as failure to meet the primary end point to a level of statistical significance. Triggering conditions might also reference deadlines for study completion. Although companies may be reticent to prespecify terms of study failure, precision is reasonable in exchange for early approval.

Together, these improvements might permit the FDA to exert greater pressure on companies to adhere to promises regarding evidence generation and withdrawal conditions. The combination of voluntary postmarket commitments, explicit waivers of hearing rights, and specific conditions for withdrawal would allow the FDA to more closely approximate the conditions of accelerated approval. However, the possibility of denying approval before adequate evidence is submitted must not be forgotten.

Conclusions

Given its apparent safety and the PHOENIX trial’s likely completion to satisfy international regulatory requirements, Relyvrio’s approval may have been justified. Nonetheless, viewing Amylyx’s statement as a true promise to withdraw is problematic and reflects a worrisome scenario in which the FDA implores companies to precommit to withdrawal rather than having adequate independent authority to rapidly remove ineffective products. To avoid FDA approval devolving into an uncritical “right to try,” the agency’s regulatory flexibility to withdraw should match its flexibility to approve.

ARTICLE INFORMATION
Published Online: December 8, 2022. doi:10.1001/jama.2022.22566
Conflict of Interest Disclosures: Ms Fernandez Lynch reported receiving grants from Arnold Ventures beginning in December 2022 outside the submitted work and serving as an unpaid member of New York University’s Compassionate Use and Preapproval Access Working Group and a paid ethics consultant to the Robert Wood Johnson Foundation. Ms Sachs reported receiving grants from Arnold Ventures and personal fees from the Institute for Clinical and Economic Review, the National Academy for State Health Policy, and West Health outside the submitted work.

REFERENCES