The FDA Struggle to Withdraw Makena Problems With the Accelerated Approval Process

Hydroxyprogesterone caproate (Makena) is an injectable drug for the prevention of preterm birth, ie, birth prior to 37 weeks of gestation. About 1 in 10 US infants is born preterm, a condition that is increasing in the US and is responsible for about 75% of perinatal mortality and about half of neonatal morbidity. The US Food and Drug Administration (FDA) approved Makena through its accelerated approval pathway in 2011. In this Viewpoint, we discuss the controversy surrounding the current efforts of the FDA to withdraw Makena from the market and the implications for the broader accelerated approval pathway.

Although clinical trials usually measure clinical endpoints, the FDA accelerated approval program, launched in 1992, speeds drug development by liberalizing the use of surrogate endpoints for serious or life-threatening conditions. In considering the use of surrogate endpoints in this pathway, the FDA is permitted to take into account the need for treatments and the severity and prevalence of a disease. However, applicants must conduct phase 4 confirmatory trials to verify clinical benefit, and poor results can lead to the withdrawal of the drug.

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It was 1975 when a small clinical trial concluded that the gestational administration of hydroxyprogesterone caproate lengthened pregnancy and reduced neonatal mortality. In the wake of additional research in this arena, then-manufacturer Adeva applied to the FDA for approval of hydroxyprogesterone caproate for reducing the risk of preterm birth in women with a history of preterm birth. The FDA granted the accelerated approval in 2011. Not everyone at the agency supported the decision. An FDA report identified several statistical problems in the single study supporting approval and concluded that “the information and data do not provide convincing evidence” of effectiveness. The report further suggested delaying approval until interim results became available from yet another clinical trial. However, in its risk-benefit calculus, the FDA indicated that it was convinced by the public health importance of preterm birth and the lack of existing treatment. Although the FDA granted accelerated approval, it required the company to proceed with a confirmatory trial, which had begun enrollment and was to be completed in 2016.

The confirmatory trial results became available in 2019, 3 years after the trial’s projected completion date. The data proved disappointing, thereby leading an advisory committee in 2019 to conclude unanimously that the new trial did not confirm clinical benefit. Three years later, the FDA is still attempting to remove Makena from the market. Although the FDA has concluded that Makena lacks substantial evidence of effectiveness, the manufacturer refused to withdraw the drug voluntarily and requested a hearing. The FDA asserted in briefing documents that continued marketing of Makena “would undermine the integrity of the accelerated approval pathway.” After a 3-day hearing in October 2022, an FDA advisory panel voted 14-1 that Makena should be withdrawn. The current manufacturer of the drug, Covis Pharma, is vigorously contesting FDA action.

The Makena story raises questions about the accelerated approval pathway’s implicit promise: approval can be provided on an expedited basis with the ability to quickly withdraw drugs that fail confirmatory trials. In this case, the delay in effectuating withdrawal has been dramatic. Although some of the delay is no doubt attributable to the emergence of COVID-19 in 2020 and its sapping of FDA resources, other elements were also at play. For the FDA to withdraw a drug, the statute and regulations require an informal hearing, which includes the convening of an advisory committee and the preparation of extensive materials for the hearing. The Makena docket has 241 documents and the hearing lasted 3 days. The FDA is expending considerable resources to build the record for withdrawal, given the possibility that the aggrieved company will ultimately take it to court. The FDA has only once before exercised its authority to withdraw an accelerated approval indication against a company’s wishes, in the case of bevacizumab (Avastin), which had been approved for use in the treatment of breast cancer. A recent bill would have attempted to facilitate withdrawals of accelerated approval by removing the informal hearing requirement. However, the proposed substitute procedure was also quite cumbersome—including notice-and-comment procedures for each withdrawal and convening of an advisory committee upon industry’s request. In any event, although the bill in question passed the House of Representatives, it “died” in the Senate.

Attempts to withdraw a drug like Makena also put the FDA in a difficult position. Despite poor confirmatory trial
results, the agency may face pressure from those who have used or want to use the drug. The FDA may also worry that physicians or patients may dodge the withdrawal by obtaining the drug from other sources, for example, through off-label use (if the drug is otherwise available) or through a compounding pharmacy. The agency also faces a potential trade-off in that some physicians may be able to tailor the use of a drug to situations wherein patients are more likely to benefit. For example, some obstetricians have moved toward using Makena only for patients who are at the highest risk of preterm birth. For example, some obstetricians have moved toward using Makena only for patients who are at the highest risk of preterm birth. However, the FDA analysis suggests that no subgroup benefits from the drug. In this case, the FDA has been uniquely vocal about its desire to withdraw its erswhile approval. Finally, withdrawal of a drug like Makena may place the FDA at odds with other agencies and organizations, potentially confusing the public. For example, the Centers for Disease Control and Prevention recommends that pregnant individuals with a history of preterm birth talk to their physicians about progesterone therapy. For patients, it is not obvious whether such a discrepancy with the FDA is due to bona fide scientific disagreement or simply the realistic lag time for an agency to update its own materials in response to a change by FDA.

The delay in withdrawing Makena has proven costly for the Centers for Medicare & Medicaid Services (CMS), which is paying for the drug, and for the patients who are exposed to adverse effects with little or no clinical benefit. Between 2018 and 2021, CMS spent more than $700 million on Makena. Makena’s adverse effects include increased risk of cancer in exposed offspring, including pediatric brain cancer. The presence of a drug like Makena on the market may also discourage other manufacturers from developing or commercializing new therapies to prevent preterm birth. Although accelerated approval can facilitate drug development in some cases, it carries serious costs when such drugs prove ineffective or unsafe. Makena also illustrates the negative impact that accelerated approval can have on evidence generation. Makena’s manufacturer had difficulty filling its confirmatory trials because US patients did not want to risk receiving placebo. It was for that reason that the manufacturer was forced to go abroad. Ultimately, 75% of patients in the confirmatory trial cohort were international. Finally, there is the cost to the FDA itself. The FDA has invested significant amounts of person-time in withdrawing the drug. This time could have been used to review other first-in-class drugs including new treatments for serious and life-threatening diseases.

What might be done? Given all the difficulties associated with the withdrawal of a drug that has gone through accelerated approval, one solution would be to require a stronger signal of efficacy before that approval is ever granted. One might worry that the more evidence the FDA requires upfront, the more the accelerated approval will devolve into a traditional approval process. This is a misunderstanding of the pathway. Accelerated approval was never meant to permit a reduction in the evidentiary standard for new drugs. Rather, it was intended to allow a more liberal use of surrogate end points. Huing closer to the pathway’s original intent may yield more dependable drugs for the US population. Congress may wish to place more guardrails on the evidence required before a drug comes to market under this pathway, for example, by reaffirming the strict requirement for 2 supportive clinical trials—only 1 was available for Makena. Some might argue that it is wiser to allow a lower evidentiary standard when there is a serious unmet health need, but the Makena case study illustrates the serious risk in permitting the sale of drugs with weak evidence of effectiveness. A different approach, as suggested by a proposed bill, is for accelerated approval to automatically expire after a defined period of time unless the FDA confirms that the approval is warranted. This would make withdrawals automatic if a sponsor fails to provide sufficient evidence to persuade the agency.

The FDA’s struggle to withdraw Makena should give pause to whether the accelerated approval pathway is living up to its promise.

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REFERENCES