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Accelerated Approval Process Is Not Without Risk: Placing Recent FDA Action in Context

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On February 23, the Food and Drug Administration (FDA) withdrew approval of Pepaxto (melphalan flufenamide), a drug that it had previously granted accelerated approval for treatment of multiple myeloma. The decision came after a post-marketing, confirmatory study of Pepaxto failed to confirm the drug's clinical benefit, and FDA determined that available evidence demonstrated that Pepaxto was not shown to be safe or effective under its conditions of use. Although accelerated approval remains an important pathway for sponsors to make treatment options for serious and life-threatening illnesses available to patients as quickly as possible, sponsors should consider the risks of marketing drugs without traditional FDA approval.

Background on Accelerated Approval

Accelerated approval is a pathway available to new drug products intended to treat serious or life-threatening illnesses that provide a meaningful therapeutic benefit over existing treatments.[1] FDA has generally required sponsors using the traditional New Drug Application (NDA) pathway to submit at least two well-controlled clinical trials as "substantial evidence" that a drug is safe and effective.[2] But accelerated approval permits FDA to approve an NDA based on clinical trial data showing either (a) an effect on a *surrogate* endpoint that is *reasonably likely*, based on epidemiologic, therapeutic, pathophysiologic, or other evidence, to predict clinical benefit, or (b) an effect on a clinical endpoint other than survival or irreversible morbidity.[3].

Sponsors of drugs granted accelerated approval are required to conduct post-marketing studies to verify and describe the drug's clinical benefit. More specifically, these studies are required to address uncertainty about the relationship between the surrogate endpoint and the clinical outcome or between the observed benefit and the ultimate outcome.[4] FDA may withdraw a drug's accelerated approval if a sponsor fails to perform the required post-marketing study diligently, the post-marketing study fails to verify the clinical benefit, any other evidence demonstrates the product is not safe or effective, the sponsor fails to adhere to any post-marketing restrictions, any post-marketing restrictions are found to be ineffective, or promotional materials are found to be false or misleading.[5]

Until 2023, the procedure for FDA to withdraw an accelerated approval was undefined, except that the sponsor was entitled to a hearing before withdrawal.[6] However, the Food and Drug Omnibus Report Act of 2022 (FDORA) formalized the procedure.[7] Now, FDA must provide the sponsor with a proposed withdrawal of approval, an explanation, and an opportunity for a meeting. FDA then must allow the sponsor a written appeal with a public comment period. After that, FDA must publish a summary of the comments and FDA's response, and, if the sponsor requests it, convene of an advisory committee.[8]

Implementation of the New FDORA Procedures in FDA's Withdrawal of Pepaxto

The Papaxto decision was the first time FDA implemented the formalized withdrawal procedure under FDORA.[9] The applicant, Oncopeptides AB, submitted an appeal and met with the FDA commissioner's designee. The appeal contended that, contrary to FDA's assertions, the post-marketing study, OCEAN, met the primary endpoint of progression-free survival (PFS).[10] Oncopeptides also claimed that the "finding of a large age-dependent heterogeneity on overall survival (OS) in the [active control] arm is highly significant and needs to be taken into consideration when interpreting the overall survival results."[11]

FDA disagreed, concluding that under the prespecified statistical analysis plan for the trial, the drug failed to demonstrate statistical superiority with respect to either PFS or OS (and in fact showed a five-month deficit for OS).[12] FDA rejected Oncopeptides' contention that a potential (non-statistically significant) two-month improvement in PFS justified keeping the drug on the market, explaining that the decrease in OS undermined that potential benefit.[13] Even under Oncopeptides' post-hoc analysis—which FDA usually considers only hypothesis generating—there was a notable detrimental effect on OS.[14] For these reasons, FDA concluded that the available evidence demonstrated that Pepaxto had not been shown to be safe or effective.[15] As a result, FDA finalized its decision to withdraw Pepaxto's accelerated approval.

FDA Does Not Withdraw Accelerated Approval Most of the Time, but It Happens More than You Might Think

Although Pepaxto was the first withdrawal of an accelerated approval under FDORA's formalized procedures, it is one of many accelerated approvals that FDA has withdrawn since creating the pathway in 1992. In fact, as shown in Table 1 below, over the course of the program, FDA has withdrawn accelerated approval of 41 out of 315 drugs (13.0%), with cancer drugs being withdrawn most frequently (14.4%). While FDA has verified clinical benefits of, and granted traditional approval to, most drugs granted accelerated approval (54.2%), a substantial number are withdrawn, and nearly one-third (32.7%) have not been converted to traditional approval and/or have ongoing post-marketing studies.

Table 1

	Status			
Accelerated Approval Type	**Verified**	**Ongoing**	**Withdrawn**	**Tot**
Infectious Disease (inc. vaccine)	45	14	9	68
Non-Malignant Hematological, Neurological, and Other	23	26	4	53
Cancer[16]	103	63	28	194
Total	171	103	41	315

Accelerated approval may be a worthwhile option for sponsors looking to get a product on the market and into patients' hands as soon as possible, but it is far from foolproof. If FDA's decision on Pepaxto is any indication, the procedures formalized under FDORA may provide a more robust record of FDA's decision to withdraw a drug's accelerated approval, but they are unlikely to substantially impact FDA's decision-making. The ultimate decision remains the same—FDA must determine whether the product has been shown to be safe and effective.

The Impact to Litigation Risk

At first glance, FDA's withdrawal of a drug's accelerated approval would seem to create a scenario ripe for litigation, with a drug removed from the market after gaining approval with less safety and efficacy data than typically required. But it appears that there have not been lawsuits—products liability, consumer class action, securities class action, or otherwise—arising directly from FDA's decision to withdraw a drug's accelerated approval.[17]

There may be reasons for that. It could be difficult to bring a claim alleging fraudulent marketing of an accelerated approval drug because, unlike for other drugs, FDA requires sponsors to submit its promotional materials to FDA as part of the NDA approval process, providing sponsors some cover for their promotional messages at product launch.[18] And label-based claims may be more difficult to prove because the label explicitly states that the product has been granted accelerated approval.

That is not to say there has been *no* litigation involving drugs granted, or seeking, accelerated approval. Securities litigation has arisen when patients experienced serious adverse events after a drug received accelerated approval, but before the completion of required post-marketing studies.[19] Shareholders have also brought securities claims for statements allegedly misrepresenting the likelihood of a drug achieving accelerated approval.[20]

The new withdrawal procedures under FDORA, implemented in the withdrawal of Pepaxto, probably do not change the risk calculus. But they do leave more of a paper trail for plaintiffs' counsel to allege lack of efficacy, and the risk of litigation—always a possibility for accelerated approval drugs—certainly has not been reduced.

Conclusion

FDA's withdrawal of Pepaxto under the new procedures implemented by FDORA likely does not represent a sea change in the accelerated approval process or the associated risks. Instead, it is a reminder that, while accelerated approval may be a good development strategy for sponsors, it is not without risk. Accelerated approval is no sure thing, even after a drug enters the market, and FDA is taking seriously its post-marketing monitoring role for drugs granted accelerated approval.

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[1] 21 C.F.R. § 314.500.

[2] *See* FDA, Draft Guidance for Industry, Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products at 4 (Dec. 2019), *available at* https://www.fda.gov/media/133660/download.

[3] *Id.* § 314.510.

[4] *Id.*

[5] *Id.* § 314.530.

[6] *See id.* § 314.530(b).

[7] *See* 21 U.S.C. § 356(c)(3)(B).

[8] *See id*.

[9] *See* https://www.fda.gov/drugs/drug-safety-and-availability/fda-issues-final-decision-withdraw-approval-pepaxto-melphalan-flufenamide*.*

[10] Oncopeptides, Rationale for Oncopeptides' appeal of CDER's Proposed Withdrawal of Pepaxto and Comments on the CDER Response Document at 1, *available at* https://downloads.regulations.gov/FDA-2023-N-3167-0012/attachment_1.pdf.

[11] *Id.*

[12] *See* Peter Marks, M.D., Ph.D., FDA, Final Decision on the Proposal to Withdraw Approval of Pepaxto (melphalan flufenamide) for Injection at 9 (Feb. 23, 2024), *available at* https://downloads.regulations.gov/FDA-2023-N-3167-0049/attachment_1.pdf.

[13] *See id.* at 10.

[14] *See id.* at 11-12.

[15] *See id.* at 13-17.

[16] FDA maintains a separate list of accelerated approvals for malignant hematology and oncology indications that have been granted for supportive care products and changes to dosing or formulation, which includes eight products, five of which have been granted traditional approval, two of which are ongoing, and one of which has been withdrawn.
See https://www.fda.gov/drugs/resources-information-approved-drugs/other-cancer-accelerated-approvals.

[17] Based on a search of Lexis for opinions and its CourtLink feature for state and federal dockets (last visited May 21, 2024).

[18] *See* FDA, Guidance for Industry, Providing Submissions in Electronic and Non-Electronic Format—Promotional Labeling and Advertising Materials for Human Prescription Drugs at 7 (Apr. 2022), *available at* https://www.fda.gov/regulatory-information/search-fda-guidance-documents/providing-regulatory-submissions-electronic-and-non-electronic-format-promotional-labeling-and.

[19] *See, e.g.*, *Liu v. Intercept Pharms., Inc.*, No. 17-cv-7371, 2020 U.S. Dist. LEXIS 53252 (S.D.N.Y. Mar. 26, 2020) (granting motion to dismiss putative securities class action arising from serious liver injuries reported after accelerated approval of Ocaliva).

[20] *See, e.g.*, *Frater v. Hemispherix Biopharma, Inc.*, 996 F. Supp. 2d 335 (E.D. Pa. 2014) (denying motion to dismiss putative class action where sponsor allegedly misrepresented, among other things, the chances its product would receive accelerated approval).

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