PINK SHEET
CITELINE REGULATORY

08 Apr 2024 | **Analysis**

Fighting Accelerated Approval Withdrawal Hinders Other Sponsors' Applications, FDA's Pazdur Says

by Sue Sutter

Resource-intensive withdrawal process means FDA reviewers are not able to work on other drugs, Oncology Center of Excellence Director Richard Pazdur says, citing the 'arduous' withdrawal of Pepaxto. Pazdur also says no one should be surprised that the FDA has begun issuing complete response letters when confirmatory studies are not sufficiently advanced.

Accelerated approval sponsors who fight the US Food and Drug Administration's request for product withdrawal are hindering the agency's ability to help other companies' drug development efforts, Oncology Center of Excellence Director Richard Pazdur said.

In a 4 April fireside chat at an industry partnering event ahead of the American Association for Cancer Research's annual meeting in San Diego, Pazdur discussed the large amount of agency resources spent trying to withdraw accelerated approval of the new drug application for *Oncopeptides AB*'s multiple myeloma drug Pepaxto (melphalan flufenamide).

Pazdur also asked sponsors to consider the "greater good" when they have been asked to withdraw an accelerated approval product because a confirmatory trial has failed to verify clinical benefit.

Key Takeaways

- Despite proceeding under FDORA's expedited measures, the Pepaxto withdrawal was an arduous process for the FDA, involving many meetings.
- A sponsor's decision to fight a withdrawal request takes time away from the FDA's review of other drug programs.
- The FDA will take a patient-centric

PINK SHEET
CITELINE REGULATORY

'Folks, That Impacts Your Drugs'

In February, Center for Biologics Evaluation and Research Director Peter Marks, serving as the commissioner's designee, ordered the NDA for Pepaxto withdrawn, marking the first test of the expedited withdrawal procedures under the Food and Drug Omnibus Reform Act. (Also see "*Accelerated Approval: US FDA's Hammer Falls On Oncopeptides' Pepaxto*" - Pink Sheet, 23 Feb, 2024.)

> approach in deciding whether a complete response letter is warranted when confirmatory trials are not sufficiently progressed at the time of accelerated approval.

Of the three cases to date in which accelerated approval sponsors have fought the Center for Drug Evaluation and Research's request for withdrawal, Pepaxto marked the shortest interval between CDER's withdrawal proposal and the agency's final order. (Also see "*Oncopeptides' Pepaxto Withdrawal Speeds Through In 7 Months Under Expedited Procedures*" - Pink Sheet, 23 Feb, 2024.)

However, the entire Pepaxto situation dragged out for years, beginning with an FDA safety alert in July 2021 about an adverse survival trend in the OCEAN confirmatory trial.

> ***"When somebody has an inferior survival that's been discussed at ODAC, with a large number of meetings explaining to the company that we cannot approve a drug with this, to really try to extend this out is tremendously resource wasteful … for the agency." – FDA's Richard Pazdur***

In October 2021, just days before a scheduled Oncologic Drugs Advisory Committee meeting on Pepaxto, Oncopeptides announced it would voluntarily withdraw the NDA at the FDA's request. (Also see "*239 Days: Oncopeptides' Myeloma Drug Pepaxto Comes Off Market Just Months After Accelerated Approval*" - Pink Sheet, 22 Oct, 2021.) However, the company reversed course several months later and rescinded its withdrawal, although Pepaxto never returned to the US market.

In September 2022, ODAC voted 14-2 that the drug did not have a positive benefit-risk profile and should be withdrawn. (Also see "*Oncopeptides' Pepaxto Needs New Study To Identify Population That Will Benefit, FDA Panel Says*" - Pink Sheet, 22 Sep, 2022.)

Pazdur said FDA staff held dozens of internal and sponsor meetings on Pepaxto. (Also see "*New Accelerated Approval Withdrawal Process More Streamlined, Marks Says*" - Pink Sheet, 26 Feb, 2024.)

Even with the withdrawal proceeding under FDORA's expedited measures, which eliminated the need for a public hearing, it was "a very arduous process," he said. "A lot of internal meetings have to occur."

"I really would ask companies to realize and look for the greater good," Pazdur said. "When somebody has an inferior survival that's been discussed at ODAC, with a large number of meetings explaining to the company that we cannot approve a drug with this, to really try to extend this out is tremendously resource wasteful ... for the agency."

"And folks, that impacts your drugs," Pazdur told the audience. "When we're working on these projects, we can't do your drugs in a timely fashion. We have X number of reviewers. And when somebody is drawing out this process, cancelling ODACs as happened here, and then calling us up and saying, 'Oh, we made a mistake, we want to continue with development.'"

The Pepaxto dispute highlighted another issue related to the FDA's withdrawal authority – delays in formalizing a product's removal by publishing a notice in the Federal Register.

"One of the problems was the agency wasn't fast enough to actually remove the drug from the market or the indication, because it requires a bureaucratic process which is arcane and should be expedited," Pazdur said. "But that allowed the company then to come back with the same NDA" after rescinding its voluntary withdrawal without having to file a new application.

'Takeaway Message' From Regeneron CRLs

On the subject of accelerated approval, Pazdur was asked by Alexander Gaffney, Politico's executive director of regulatory policy and intelligence, the session's host, about the FDA's recent issuance of complete response letters to *Regeneron Pharmaceuticals, Inc.* for odronextamab in two lymphoma indications. Regeneron said the CRLs related solely to the timeline of the ongoing confirmatory trials. (Also see "*Regeneron Oncology Setback Delivered By US FDA Crackdown On Accelerated Approval*" - Pink Sheet, 25 Mar, 2024.)

This is believed to be the first time the FDA has issued a CRL strictly related to the status of a confirmatory trial. Regeneron said it has started the Part 1 dose-finding portion of the OLYMPIA Phase III program, but not the Part 2 confirmatory portion.

The FDA's oncology office has been taking a hard line with sponsors in recent years on ensuring that confirmatory trials are up and running, and preferably in an advanced state, at the time of accelerated approval. (Also see "*FDORA Effect? For Accelerated Approval Class Of 2023, Most*

Confirmatory Trials At Least Underway" - Pink Sheet, 29 Jan, 2024.) FDORA, which was enacted in December 2022, gave the agency authority to require confirmatory studies be ongoing at the time of approval. (Also see "*A Greater Power: US FDA May Become More Insistent On Timing Of Accelerated Approval Confirmatory Trials*" - Pink Sheet, 25 Jan, 2023.)

> ***"We've been telling companies they need to come and talk to us about a comprehensive development plan from day one. We are not asking for more. We are asking for a different timing of this." – FDA's Richard Pazdur***

Pazdur previously has said the FDA is working on a guidance to define what ongoing means in this context, and that an oncology product will not receive accelerated approval unless there is a confirmatory trial underway. (Also see "*Accelerated Approval: US FDA Writing Guidance On What 'Ongoing' Means For Confirmatory Trials*" - Pink Sheet, 15 Nov, 2023.)

"The takeaway message" from the Regeneron CRLs "is that we have been talking about this for more than a decade," Pazdur said. "This should come to nobody as a surprise."

He pointed to data indicating that the "problem children" among accelerated approval drugs, meaning those that were much delayed in confirming clinical benefit, were those for which confirmatory trials were not ongoing at the time of approval. (Also see "*Accelerated Approval: Sponsor Size No Excuse For Confirmatory Trial Delays, FDA Says*" - Pink Sheet, 18 Nov, 2023.)

"We've been telling companies they need to come and talk to us about a comprehensive development plan from day one," Pazdur said. "We are not asking for more. We are asking for a different timing of this."

Discussions about what the accelerated approval and confirmatory study will be need to take place "on that first visit when you mention the word accelerated approval, because we really want these programs to be occurring in tandem," Pazdur said. "We do not want to have a sequential approach where one gets an accelerated approval, and oh, by the way, they might start discussing with us after the approval the confirmatory study."

Patient-Centric Approach To Confirmatory Trial Status

The agency will take a patient-centric approach in deciding whether to issue a CRL due to the status of the confirmatory trial, Pazdur said, describing some of the factors the FDA will

consider.

“If we really believe that there are no other therapeutic alternatives, then there will be obviously some degree of flexibility,” Pazdur said. “When we do see, however, that there may be accelerated approval with the same class of drugs, with the same diseases, and with sponsors previously having most of the confirmatory study accrual already completed at the time of accelerated approval, we have to have a level playing field for all of the pharmaceutical companies.”

OCE wants companies to have the confirmatory studies ongoing at the time of approval, “and that means that the actual studies are ongoing,” not just the dose-finding portion of a trial, he said.

Pazdur suggested the agency also will take a close look at the state of confirmatory studies involving combination use of the drug. In a January interview with the *Pink Sheet*, Pazdur said there have been cases where the drug is intended to be used in combination in a confirmatory trial, but there have been challenges in combining two drugs, resulting in the studies falling further behind. (Also see "*Pazdur On Accelerated Approval: FDA Needs To Explain Why It Does Not Always Seek Withdrawal When Trials Fail*" - Pink Sheet, 30 Jan, 2024.)

“A lot of the work needs to be done beforehand,” he said. “It’s a case-by-case basis that we'll be looking at, but the studies have to be enrolling, and we have to have confidence that these studies will meet prespecified timelines.”

“There should be some comfort that we have in discussion with the companies that the trial will meet accrual goals,” Pazdur said. “And that can only be accomplished by having at least some … enrollment in the clinical trial, the exact number of that needs to be discussed.”

Pazdur suggested there is no excuse for an oncology sponsor not to understand the FDA’s expectations for ongoing confirmatory studies.

“People have felt that they could skirt the issue, or we were going to be asleep at the switch,” he said. “But I think those people that are saying that they didn't know about this, it's really an excuse because they're caught with their pants down … to be blunt.”

Furthermore, Pazdur is tired of hearing excuses.

“Companies always come to us and say, ‘Oh, we don't have enough funding to do this study,’” he said. “That argument falls on deaf ears. Don't even bother wasting your breath discussing that with us because we do not get involved with the finances here of a particular company. Again, we have to have a level playing field, whether we're dealing with a large pharmaceutical company or

a tiny biotech company. If you don't have the funding for it, to put it in the vernacular, maybe you shouldn't be in the business."