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A Greater Power: US FDA May Become More Insistent On Timing Of Accelerated Approval Confirmatory Trials

by Sue Sutter

Bolstered by new statutory authority and the Oncology Center of Excellence's experience in pushing for early initiation of confirmatory trials, review divisions may take a tougher line with sponsors on the design and timing of studies to verify clinical benefit.

Drug and biologic product sponsors should anticipate that US Food and Drug Administration review divisions will become more insistent in 2023, though perhaps not absolute, about the need for confirmatory trials to be underway at the time a product receives accelerated approval.

The agency's new authority under the Food and Drug Omnibus Reform Act to require that studies be started prior to approval, or within some specified period of time thereafter, may embolden reviewers to take a harder stand with sponsors when it comes to confirmatory trial planning and initiation, although much will depend on the product itself and the therapeutic setting, experts said.

In addition, the Oncology Center of Excellence has taken aggressive and proactive measures in recent years to ensure confirmatory trials are not compromised by a product's accelerated approval, and that the so-called "period of vulnerability" between market entry and verification of clinical benefit is as narrow as possible. (Also see "*US FDA Says Confirmatory Trials Should Start Before Accelerated Approval But Is Not 'Dogmatic'*" - Pink Sheet, 30 Nov, 2022.)

In staking out this leading position, OCE and the oncology review divisions have created a model that reviewers in other therapeutic areas increasingly may adopt going forward, experts said.

US FDA Has History Of Pushing

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"I think the sponsor, in most cases, should be in a position to have designed their confirmatory trials prior to accelerated approval, because that should be an integral part of their clinical development program," said Geoffrey Levitt, of counsel at DLA Piper in Washington, DC. "And that's what the FDA, I think, is saying. Oncology has often taken the lead in some of these areas within the agency. I do suspect that this is going to become more of the common ground going forward."

Sponsors On Confirmatory Trials … Sometimes

By Sue Sutter

25 Jan 2023

Even before a new law granted FDA authority to require studies be underway before accelerated approval, review divisions have, in some cases, given sponsors years of advance notice on expectations around study timing, according to a *Pink Sheet* review of NME accelerated approvals.

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With the new legislative power on confirmatory studies, coupled with clear goals under the prescription drug user fee program around communicating with sponsors on postmarketing requirements, "I think it's quite possible that that we will see this more often, that FDA will use its codified authority … in ensuring that studies are underway," said Krista Carver, a partner at Covington and Burling in Washington, DC.

FDA Practice Codified In Omnibus

The FDA's regulations on accelerated approval of drugs and biologics state that postmarketing studies to verify clinical benefit "would usually be studies already underway" at the time of approval.

The FDA's May 2014 guidance on expedited programs for serious conditions states that if it is clear during development that a product is intended to be approved under accelerated approval on the basis of a surrogate endpoint or an intermediate clinical endpoint, confirmatory trials should be underway at the time the marketing application is submitted.

If it is not clear until shortly before or after application submission that a surrogate endpoint or an intermediate clinical endpoint will be the proposed basis for accelerated approval, there should be agreement on the design and conduct of such trials before approval, the guidance states.

A review of new molecular entities and novel biologics that received accelerated approval from 2020-2022 shows varying levels of FDA staff attention, as documented in publicly available review documents, to the status of confirmatory trials before and during the application review process. *(See sidebar for story.)*

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In some cases, particularly in oncology, review staff have been quite forceful about the need for studies to be underway at the time of submission or approval. The agency now has legislative authority to demand as much.

The omnibus appropriations bill enacted at the end of 2022 states that the FDA "may require, as appropriate," that confirmatory studies be underway prior to approval "or within a specified time period after the date of approval." (Also see "*Accelerated Approval Reforms Give US FDA More Power And Flexibility – With Some Gaps*" - Pink Sheet, 20 Dec, 2022.)

The FDA said it is currently considering and working to implement the new statutory provisions related to accelerated approval and did not have additional information to share at this time.

'May,' Not 'Must'

Experts noted the importance of the statutory language that the FDA "may" require studies be underway at the time of accelerated approval, not that it "must."

"I view that authority as codifying existing FDA regulations and guidance and confirming that FDA has flexibility to allow approvals both before and after the confirmatory trial is initiated," Carver said.

"I think from a public health perspective that that's a good approach to ensure that patients with serious conditions can get timely access to therapies, even if the accelerated approval approach becomes evident later in the development and review process," she said.

"I do think it's critical that the statute retains the agency the flexibility to decide that's not appropriate in a particular case," such as "where there has been a lot of back and forth on the confirmatory study design such that it's not realistic to expect that the study would have started at the time of approval and patients should not be denied access to what otherwise would be a safe and effective therapy because of that issue."

"But on the other hand, we understand that it was important to the agency that it have clear authority to require studies would be underway at the time of approval where appropriate," Carver said. "That was something that was reflected in agency regulation and guidance already. So I think industry is familiar with that approach."

"There's room for the agency to exercise its discretion," said Jacqueline Berman, a partner at Morgan Lewis in Washington, DC. "Like many things in the clinical development process, it will likely be part of a discussion with FDA. And so, like any discussion with an agency, sponsors should be thinking about what might serve their product and what might serve their patient population best when going into those discussions."

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> *"There could be situations in which the FDA wants to really make sure that confirmatory trial is underway, and it really should be." - Hyman, Phelps and McNamara's Frank Sasinowski*

Berman said it will be important to see which review divisions end up flexing this new authority and requiring that confirmatory studies be underway at the time of approval. When asked whether the FDA might issue a complete response letter simply because a confirmatory trial has not yet begun, Berman replied: "That's a really interesting question to ponder."

Frank Sasinowski, a director at Hyman, Phelps and McNamara in Washington, DC, also expects the decision on whether to leverage this new authority will be a case-by-case determination depending upon the specific therapy and disease at issue.

In some situations, the agency may be concerned that a confirmatory trial cannot enroll once a product becomes available under accelerated approval in the US, he said. "There could be situations in which the FDA wants to really make sure that confirmatory trial is underway, and it really should be."

Sasinowski does not see the new authority as representing a sea change but more "embodying what already is on the ground."

"Over the years, even without this new statute, there's been a tendency for the FDA to be more careful about ensuring that a sponsor is going to have a study that the FDA has agreed to, so that the design has been hammered out and maybe they've started to enroll."

The omnibus legislation, including the new accelerated approval council created under the law, could help bring more consistency to the FDA's approach on confirmatory trials, experts said.

"Accelerated approval is a big, big thing in the neurodegenerative area," Levitt said. "But I think by the same token, you can't have a situation where one division of FDA is applying a different framework. Over any given period of time, one division can take the lead. Over an extended period of time, it's going to become more and more obvious if different divisions are playing different paradigms."

Marrying FDORA And PDUFA VII

An important implementation issue will be how the agency marries this new authority under FDORA with the new performance goals on postmarketing requirements under the seventh

iteration of the Prescription Drug User Fee Act, Carver said.

In the PDUFA VII commitment letter, the FDA agreed to establish processes to support consistency and predictability throughout the identification, determination and evaluation of postmarketing studies.

For NME new drug applications and biologics license applications, the FDA will communicate details on anticipated PMRs, including studies required as a condition of accelerated approval, no later than six and eight weeks prior to the action date for priority and standard applications, respectively.

These communications will summarize the agency's preliminary evaluation of required postmarketing studies, including the study purpose, critical study design elements including type of study and study population, and timelines for discussions and engagement on the PMR for the remainder of the review cycle.

The performance goals for these communications will be phased in, starting at 60% of NMEs in fiscal year 2023, 70% in FY 2024, and 80% in each of the next three fiscal years.

The FDA also will update all relevant Manuals of Policies and Procedures (MAPPs), Standard Operating Procedures and Policies (SOPPs), and guidances regarding the preapproval processes for establishing PMRs.

"I think that it's very important that FDA ensure that it has a process in place that enables streamlined and timely feedback on postmarketing requirements to make the codified approach on postmarket study requirements work," Carver said.

The six- and eight-week intervals for PMR communications prior to approval are "a pretty tight timeline to get everything into place for a postmarketing study and make sure that it's able to timely start," Carver said. "And so I think it's all the more important that that those goals be met and that FDA aim to, in a very timely fashion, communicate with sponsors about these studies so they can be started as soon as possible."

A New Look To Confirmatory Trials

The OCE experience and the new legislative authority also could recast the look and design of some confirmatory studies.

OCE increasingly has been encouraging the concept of a single randomized study with a primary endpoint that can serve as the basis for accelerated approval, and secondary endpoints that can provide the needed confirmatory evidence postapproval. (Also see "*'On-And Off-Ramps' For Cancer Accelerated Approvals: FDA Suggests Earlier Randomized Trials*" - Pink Sheet, 21 Sep,

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2022.)

There are pros and cons to this approach, Berman said.

On the plus side, a sponsor does not have to design a separate trial, and the FDA is assured that the confirmatory evidence is being gathered, with there having been prior discussions around the design of that study.

However, one of the cons of this approach is that at the time of the application for accelerated approval, "not only is the FDA going to look at that primary endpoint, but there's also potential for the agency to start looking at incomplete data from that secondary endpoint, which really isn't fully developed" yet, such as an overall survival endpoint, Berman said, adding that this can present some challenges for sponsors.

Whether there will be a bigger shift in non-oncology settings toward his approach, and away from the traditional stepwise approach of discrete trial phases, will depend a lot on the disease state, because some diseases and endpoints might not lend themselves to this more blended approach, Berman said.

Nevertheless, "I would not be surprised if we see that. And I think we're seeing that generally, separate and apart from the issue of accelerated approval," she said. "We're starting to see studies be extended, such that what started as a Phase I study becomes a Phase II study becomes a Phase III study, especially in some of these areas where it might be a rare disease state. So it wouldn't surprise me if there's more of a blending of the confirmatory study and the pivotal study, but it really will be a product-by-product issue, I think."

Keeping A Closer Eye On Progress

A provision in the omnibus that requires accelerated approval sponsors to file confirmatory trial progress reports every six months, rather than annually, could help the agency keep a closer eye on situations where confirmatory trials are having difficulty enrolling after accelerated approval.

It also could prompt the agency to question whether a sponsor is dedicating adequate resources to a confirmatory trial.

Two Years In US Accelerated Approval Withdrawals

By Sue Sutter

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Twenty accelerated approval indications have been voluntarily withdrawn by sponsors since December 2020, most coming as a result of the FDA cancer office's push to rid labeling of

The legislation makes the failure of an accelerated approval product sponsor to conduct with due diligence any required postapproval study, or to submit timely progress reports, prohibited acts under the Food, Drug and Cosmetic Act. This could open sponsors up not only to product withdrawal, but also civil and criminal penalties under the FDCA, Berman said.

‘dangling’ and ‘delinquent’ indications that lack confirmation of clinical benefit.

Read the full article here

“It'll be interesting to see whether that ever actually gets exercised,” Berman said. “It certainly provides more teeth to some of the provisions than were there before, and it's something that I think folks should be mindful of.”

Several of the 20 accelerated approval indications voluntarily withdrawn in the past two years have been the result of “delinquent” confirmatory trials that were never completed or, in some cases, never started. (*See sidebar.*)

Brenda Sandburg contributed to this story.