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Sarepta Pressured FDA On Eteplirsen Due To 'Dire' Finances, Gave Investors Rosier Picture

by Derrick Gingery

Emails reveal company wanted timelines and approval commitments from FDA toward the end of the eteplirsen review, saying it might not be able to continue studies; at the same time, Sarepta was telling investors it had 12 months of cash on hand.

Sarepta Therapeutics Inc. tried using company financial problems to push FDA to complete the final stages of the review of the Duchenne muscular dystrophy drug *Exondys 51* while also telling investors there was enough operating capital to continue for a year.

The move did not work because FDA's approval was delayed several months after officials appealed the final decision made by Center for Drug Evaluation and Research Director Janet Woodcock. But the emails exchanged between FDA and Sarepta officials could partially explain why the company's financial health, which the agency normally would not consider, became an issue in the decision to approve the product.

Emails, memos and other documents related to the review of Exondys 51 (eteplirsen) indicate that in June, after FDA asked for additional dystrophin data from Sarepta, the company requested that the process be started quickly. Sarepta also asked FDA to confirm that the drug would be approved by the end of that month once the required increase in dystrophin was shown.

Shamim Ruff, Sarepta senior vice president of regulatory affairs and quality, wrote in a June 2 email that the company could complete the requested additional biopsies and dystrophin analysis by the end of that month, assuming the process goes perfectly the first time, but the process had to begin by June 6.

"There is no room for flexibility with this date due to our dire financial constraints as a result of the ongoing delays," Ruff said.

The original review goal for the product was Feb. 26, but it was moved to May 26 after Sarepta submitted additional data following release of FDA's advisory committee materials. (Also see "*Sarepta's Duchenne Treatment Likely Making Progress At FDA*" - Pink Sheet, 8 Feb, 2016.)

FDA also missed that deadline in asking for more dystrophin data after the advisory committee meeting. After the panel voted against recommending approval, the agency requested more biopsies from the ongoing PROMOVI trial. (Also see "*Priority Review Politics: With Two Pending DMD Products, FDA Still Faces Community Anxiety*" - Pink Sheet, 18 Aug, 2016.)

Delays Could Impact Study Completion

Ruff's June 2 message did not provide more detail on the company's financial issues that were referenced.

Later in the email, Ruff also asked that "FDA will confirm – by June 3, in writing, that accelerated approval will be granted by the end of June when an increase in dystrophin is demonstrated ..." She also said that further delays could impact the company's ability to complete the clinical studies for Exondys 51.

"Labeling discussions and post-marketing commitments to be conducted concurrently and completed by the end of June or sooner," Ruff wrote. "Any delay, for any reason, past June will significantly impact our ability to continue the ongoing eteplirsen studies."

It would appear that Ruff's comments resonated with Woodcock.

Woodcock sent a "General Advice" memo to the company dated June 3 that said if the analysis of the new biopsies showed a meaningful increase in dystrophin using Western blot analysis, "we expect to be able to grant an accelerated approval within four business days of receiving the data (assuming all other aspects of the application are approvable)."

She also asked that Sarepta refrain from publicly communicating "specific details of this plan until after completion in order to allow maximum procedural efficiency."

The company's attempt to speed the approval did not succeed, however. FDA did not announce Exondys 51's approval for treatment of Duchenne in patients amenable to exon 51 skipping until Sept. 19. (Also see "*Sarepta's Eteplirsen Approved After Contentious Internal FDA Debate*" - Pink Sheet, 19 Sep, 2016.) The product launched immediately after the approval, which included post-marketing confirmatory trials. (Also see "*Sarepta Must Balance Exondys 51 Confirmatory Trials And Sales*" - Scrip, 23 Sep, 2016.)

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The disagreement between FDA staff led to a formal appeal process that eventually reached Commissioner Robert Califf. As part of that process, Woodcock suggested that Exondys 51 may need to be approved for Sarepta's financial health and to promote drug development in Duchenne, and Califf said he was troubled by the comments. (Also see "*Woodcock's Consideration of Sarepta Financial Issues Raises Eyebrows*" - Pink Sheet, 19 Sep, 2016.) But he deferred to Woodcock's judgement, in part because he did not want a political appointee affecting the approval process. (Also see "*Political Appointees Shouldn't Influence Approval Decisions, Califf Says*" - Pink Sheet, 20 Oct, 2016.)

Exondys Approval: FDA Commissioner's Draft Decision Drew Internal Rebuke

By Sue Sutter

03 Nov 2016

Even at the final step, FDA's review of Sarepta's Duchenne muscular dystrophy drug remained collaborative and contentious, as Commissioner Califf's view that accelerated approval would not set a new precedent drew pushback from ODE I Director Unger, while Acting Chief Scientist Borio said the draft decision downplayed the 'miniscule' amount of dystrophin with eteplirsen.

Read the full article here

Sarepta Thought Biopsies Could Take Awhile

Ruff's email to Woodcock followed a teleconference that morning. Sarepta requested the meeting with Woodcock and Richard Moscicki, CDER deputy center director for science operations, because it could not meet the dystrophin data request "in a timely manner."

"Please note that even if a protocol amendment is not required, it would take us several months to analyze the PROMOVI samples," Ruff wrote in a June 1 email.

FDA questioned the methods used to gather and analyze muscle biopsies to show Exondys 51 induced dystrophin production. Reviewers also raised a number of concerns about whether the amount of dystrophin that Exondys 51 produced was in fact significant and whether the boys in the clinical trials were improving. (Also see "*Duchenne Muscular Dystrophy: Second Product Isn't The Charm*" - Pink Sheet, 15 Jan, 2016.)

Company About To Raise Money At Same Time

Ruff's statement about Sarepta's financial problems does not appear to entirely agree with the company's statements to investors at that time.

Sarepta's quarterly report filed with the SEC for the period ended March 31 stated that while the company had not generated any revenue from product sales to date, it had enough resources to fund its current operational plan for another 12 months.

Its SEC filing for the first half of 2016, which ended June 30, included a similar statement that its cash, cash equivalents and investments were sufficient to fund the operational plan for "at least" the next 12 months.

And about a week after Ruff's email (June 8), the company announced it was raising another $37.5m before expenses through a stock sale, which was completed later that month.

Proceeds were to be used "principally for product and commercial development, manufacturing, any business development activities and other general corporate purposes," according to the press release. Sarepta did not respond to a request for comment on the differing views in the email and SEC filings.

SEC Investigating Exondys 51 Competitor

In the wake of the approval, a number of FDA officials, including Woodcock, have warned against trying to repeat the development model Sarepta used. FDA said the approval involved the maximum amount of flexibility allowed. (Also see "*No More Sarepta-Like Development, FDA Officials Say*" - Pink Sheet, 20 Oct, 2016.)

Califf also has said he wants to better outline FDA's interpretation of the accelerated approval regulations to increase sponsor and public understanding. (Also see "*Accelerated Approval Should Be Less 'Wide Open,' Califf Says*" - Pink Sheet, 20 Oct, 2016.)

But one investor has said that his firm already is receiving pitches for development programs similar to Exondys 51. (Also see "*FDA's Fears Realized: Sponsors Pitching Investors 'Sarepta Model'*" - Pink Sheet, 25 Oct, 2016.)

Sponsors of other Duchenne drugs that have not fared well with FDA also are appealing or considering appealing the decisions. (Also see "*Sarepta's Shadow: BioMarin Mulls Turning The Extraordinary Into A Template*" - Pink Sheet, 15 Oct, 2016.)

BioMarin Pharmaceutical Inc., which received a complete response letter after review of its proposed Duchenne product drisapersen, also is dealing with an SEC subpoena related to the product.

The company's Nov. 3 quarterly SEC filing stated that the commission is seeking documents "in connection with a non-public, fact-finding inquiry related to its former drisapersen program." BioMarin also stated that the letter accompanying the subpoena says that the action is not an indication the company broke the law. The company intends to cooperate fully with the investigation, according to the filing.