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

by Sue Sutter

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.

FDA officials involved in the dispute over whether to approve *Sarepta Therapeutics Inc.*'s *Exondys 51* (eteplirsen) did not hold back their criticisms when FDA Commissioner Robert Califf circulated his draft decision supporting accelerated approval for the Duchenne muscular dystrophy drug.

Office of Drug Evaluation I Director Ellis Unger questioned Califf's conclusion that Center for Drug Evaluation and Research Director Janet Woodcock had considered all relevant scientific evidence in deciding to grant accelerated approval. Unger further disagreed with Califf's view that the decision to approve eteplirsen would not set a precedent and lower the standards for accelerated approval.

> ***Granting accelerated approval to drugs that show "a mere scintilla" of an effect on a surrogate endpoint is an approach that "should receive broader public (and FDA) input before being implemented." – ODE I Director Unger***

"Perhaps granting accelerated approval to drugs that show a mere scintilla of an effect on a surrogate endpoint represents a stroke of brilliance – one that will stimulate investment in the development of drugs" for rare neurological disorders, Ellis wrote in a Sept. 14 email to Califf. "But in my opinion, this approach should receive broader public (and FDA) input before being implemented.

Separately, Acting Chief Scientist Luciana Borio said Califf's draft memo seemed to "downplay the significance of the very small amount of dystrophin reported in the eteplirsen NDA."

The Unger and Borio emails, along with other review documents, provide a deeper look at how the dissension over eteplirsen's approvability reached the highest ranks within FDA.

Among the newly released documents are emails between FDA and Sarepta, including one in which the company asserted it was facing "dire financial constraints" due to review delays and demanded written assurance from top CDER staff that accelerated approval would be forthcoming if data from an ongoing study showed an increase in dystrophin. (Also see "*Sarepta Pressured FDA On Eteplirsen Due To 'Dire' Finances, Gave Investors Rosier Picture*" - Pink Sheet, 3 Nov, 2016.)

Dispute Goes To The Commissioner

FDA granted accelerated approval Sept. 19 to Sarepta's antisense oligonucleotide for treatment of patients who have a confirmed mutation of the Duchenne muscular dystrophy (DMD) gene that is amenable to exon 51 skipping. The decision to approve was made by Woodcock over the objections of the Division of Neurology Products review team, other review disciplines and some high-ranking CDER officials. (Also see "*Sarepta's Eteplirsen Approved After Contentious Internal FDA Debate*" - Pink Sheet, 19 Sep, 2016.)

Unger, who heads the office that oversees the neurology review division, submitted a scientific dispute resolution appeal challenging Woodcock's decision. Unger and Woodcock disagreed as to whether the quantity of dystrophin produced by eteplirsen in clinical trials is an effect that is "reasonably likely" to predict clinical benefit, such that it can serve as a surrogate endpoint supporting accelerated approval.

Unger said that although there was evidence from interim data in ongoing Study 301 that eteplirsen induces dystrophin production in muscle cells, the effect size was inadequate, with a mean increase of 0.3% and a range of 0-1.3%. Rather, dystrophin levels of 10% or more would be needed to affect the clinical course of DMD, the ODE I director concluded.

Woodcock rejected the idea of a minimum 10% threshold and said Western blot analyses of Study 301 results clearly showed that the drug increased dystrophin production in some patients.

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Unger's appeal went first to the agency's Scientific Dispute Process Review Board, which is chaired by Borio, and then to Califf.

In his Sept. 16 final decisional memo, Califf deferred to Woodcock's judgment and authority on accelerated approval. The commissioner said he lacked the technical expertise beyond those individuals already involved the decision and the record contained adequate evidence to support Woodcock's conclusion.

In a recent speech, Califf said career scientific staff at the agency, not political appointees like himself, should make such approval decisions. (Also see "*Political Appointees Shouldn't Influence Approval Decisions, Califf Says*" - Pink Sheet, 20 Oct, 2016.)

Unger Finds Fault With Conclusions On Process …

On Sept. 13, Califf sent his draft decision to Woodcock, Unger, Borio and Office of New Drugs Director John Jenkins, requesting they advise him of any "significant factual errors" by close of business the following day.

In his email accompanying the draft, Califf said he had concluded that all applicable processes and procedures were followed in the decision-making on the drug's approval, the appealing parties had ample opportunity to present their views, and the decision to grant accelerated approval was made following consideration of all relevant scientific evidence.

> *Commissioner Califf asked agency officials to identify any "significant factual errors" in his draft decision.*

Unger, however, begged to differ.

"I have concerns with respect to two areas of your memo," Unger told Califf in a Sept. 14 email.

"First, whether proper procedures were followed such that all evidence and analyses were reviewed by the center director before a decision was rendered, and second, whether this decision will set a general precedent – where accelerated approval could be provided for a rare disease based solely only on the medical and scientific judgment/opinion of the center director, as was clearly the case here," Unger said.

Woodcock had made up her mind on accelerated approval before Unger, the signatory authority for the application, had completed his review, he noted.

Unger said that in drafting his complete response memorandum he took note of "ambiguities and discrepancies" in the immunohistochemistry results from Study 201/202, the exploratory Phase I/II study that served as the basis for the NDA submission.

"I realized that the original analysis for Study 201/202 showed 13% positive muscle fibers at baseline, whereas a subsequent analysis found only 1.1% positive fibers," Unger said. "For the three patients whose baseline tissue blocks were analyzed on two occasions, the immunohistochemistry results differed by an order of magnitude. Unfortunately, this disparity had not been addressed adequately by the review team, and had not been described at the April 25, 2016, advisory committee meeting."

"This discrepancy, raising important doubts about all of the immunohistochemistry data, was not known to Dr. Woodcock at the time she filed her approval memo on 7/14/16," Unger continued. "Her issuance of a decisional memorandum prior to careful consideration of my final review represents a critical deviation from protocol."

Sarepta's inability to reproduce its own findings with respect to the immunohistochemistry analyses "raises considerable doubt about any ability to relate and compare the dystrophin values obtained by the applicant to those reported in the literature," Unger said.

Furthermore, Sarepta had stated at the advisory committee meeting that it would be inappropriate to compare the firm's data from Western blot analyses to that reported in the literature "due to significant methodological differences."

"Therefore, there is no way to reach a rational conclusion that the dystrophin detected by the applicant, by either immunohistochemistry or Western blot, is 'reasonably likely to predict clinical benefit,'" Unger said. "There is no way to correlate a mean increase of 0.3% (median increase = 0.1%) to an effect on physical function, based on clinical experience external to the development program."

The regulatory record should reflect that there was "no scientific basis underlying the conclusion of 'reasonably likely' in this case. This was simply a judgment call by Dr. Woodcock," Unger said. The CDER director "might have also taken the position that, in this desperate patient population, any dystrophin production would suffice as a basis for accelerated approval, but she didn’t state this."

... And Precedent

Unger also took issue with Califf's conclusion in the draft memo that eteplirsen is a “unique

situation that will not set a general precedent" for accelerated approval. (Also see "*Accelerated Approval After Eteplirsen: A Lowered Bar Or A Unique Event?*" - Pink Sheet, 20 Sep, 2016.)

"We all agree that each situation must be evaluated on its own merits; however, I fail to see how DMD differs intrinsically from other rare neurological diseases, e.g., Alexander disease, Canavan disease, Early infantile GM1 gangliosidosis, Krabbe disease, Metachromatic leukodystrophy, Niemann-Pick disease, Pelizaeus-Merzbacher disease, Pompe disease, Sandhoff disease, and X-linked adrenoleukodystrophy," Unger said.

"Based on what you have written in your draft memo, it is not clear to me why a standard of any increase in the surrogate endpoint wouldn't apply for these diseases," he said.

In Unger's view, Califf's draft memo seemed to suggest that the reasonably likely standard for accelerated approval need not include any type of quantitative component.

"We all agree that making a reasonable amount of dystrophin would provide a sound basis for accelerated approval. But the amount here – a median value of one part in a thousand that is not perceptibly greater than none – fails to meet the 'reasonably likely' test," he said.

Borio: Focus On 'Crux' Of Disagreement

Borio, who shared Unger's view on the underlying scientific matters, also took issue with Califf's failure to address the small amount of dystrophin production seen in the eteplirsen trials.

"Your draft decisional memo never once cites the 0.3% increase in dystrophin production shown by Study 301 (or the 0.93% detected in Studies 201/202)," Borio said in a Sept. 14 email to Califf.

The draft attributed the scientific disagreement to a lack of consensus on the appropriate threshold for clinical benefit, both within CDER and in the scientific literature, as well as to concerns about the correlation between dystrophin production and clinical outcomes in Study 201/202, Borio said.

> ***Acting Chief Scientist Borio raised concerns that the draft decision downplayed "the significance of the very small amount of dystrophin reported in the eteplirsen NDA."***

"To me, the crux of the disagreement is not whether there is an appropriate threshold, but whether such a miniscule amount of dystrophin is reasonably likely to predict clinical benefit," she said. "Your draft decisional memo does not address that issue. In my view, it is not sufficient to say that no threshold has been established and that, therefore, any increase in dystrophin production is reasonably likely to predict clinical benefit."

Although FDA declined to provide Califf's draft memo, it appears the commissioner did take Borio's suggestions into consideration in writing the final version.

The final memo notes that the key points of disagreement were whether the amount of dystrophin produced is sufficient to be reasonably likely to predict a clinical benefit. It also reflects Unger's view favoring a 10% threshold, and Woodcock's position that FDA should exercise its greatest flexibility possible while remaining within its statutory framework.