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Internal FDA documents reveal a familiar story for Sarepta

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The unexpected approval of Vyondys 53 followed an FDA power struggle, and turned on a vague commitment from Sarepta, it has emerged.

Scott Gottlieb was right to move to rebut claims that the US FDA was approving drugs too fast; after all, he had headed up the agency at a time when its standards were allegedly falling. However, the debacle over the approval of Sarepta's Vyondys 53, revealed in newly published documents last night, undoes much of his spirited defence.

Vyondys was unexpectedly greenlit in December, four months after being rejected via a complete response letter. That U-turn, it now appears, followed extensive internal FDA disagreement, some of it reminiscent of the 2016 approval of Sarepta's other highly controversial Duchenne muscular dystrophy drug, Exondys 51.

As for clinical data, the only thing regulators reviewing the Vyondys filing had to go on was surrogate endpoints, and even these barely supported efficacy. The drug, like Exondys, received accelerated approval theoretically contingent on a confirmatory trial (*The Gottlieb legacy: a surge in unproven treatments?, March 6, 2019*).

Of course, the FDA normally does not publish complete response letters (CRLs), but if the drug in question is subsequently approved these are made public along with other relevant correspondence.

This is how investors yesterday learned the details of the FDA's CRL, Sarepta's appeal against it, and the final approval decision overturning that initial ruling. And perhaps the most remarkable passage in the CRL concerned not Vyondys but Exondys, and the precedent set by the latter drug's approval.

No confirmation

Sarepta's failure to start a confirmatory study to back Exondys's accelerated approval was "very concerning to the FDA and ... the public", the agency wrote. "As of today, exactly two years and 11 months after [Exondys's] approval, you have not initiated the required confirmatory trial."

Despite this poor precedent, the final approval for Vyondys came having only extracted from Sarepta the following commitment: "If it is concluded that the results of the confirmatory study do not support a clinical benefit Sarepta will voluntarily withdraw [Vyondys] from the market."

Additionally, two major sticking points of the CRL – preclinical kidney toxicity and infection risk at intravenous

infusion ports – are swiftly dismissed. The former can be addressed by renal function monitoring, while the latter need merely be considered in Vyondys's risk-benefit balance, the approval summary states.

Stein vs Unger vs Woodcock

It is this document that reveals FDA discord harking back to the review of Exondys. The Vyondys CRL was issued by Dr Ellis Unger, director of the agency's office of drug evaluation, but the approval rubbishing Dr Unger's concerns came from the relatively recently appointed director of the office of new drugs, Dr Peter Stein.

It was Dr Unger who in 2015/16 had clashed with Dr Janet Woodcock, the FDA's then drug review chief. Dr Woodcock had gone against expert advice to approve Exondys, and Dr Unger, who at the time reported to her, disagreed so strongly that he filed a formal dispute about the way that decision had been reached.

And Dr Unger's office is, as of November 4, being restructured, implying that he no longer had input into the ultimate Vyondys approval.

Power struggles aside, the influence of Duchenne patient groups should also not be underappreciated. These were extremely vocal when Exondys was under review, and it might be that the agency wanted to avoid a similarly damaging distraction a second time.

The fact remains that, despite the FDA's insistence, Sarepta has only this month started a confirmatory Exondys study. In the case of Vyondys such a trial was already under way: Essence has an expected completion date of May 2022.

Still, the commitment to pull Vyondys can easily be circumvented. After all, if a trial is never allowed to read out it can never be said to have failed.

This story has been corrected to reflect the current status of Exondys's confirmatory trial.