PharmaVoice

FDA's 'ivory tower thinking' ignores promising biomarkers, says a rare disease CEO

The FDA wouldn't review a drug that was 90% effective. In rare diseases, this is too common, said Ultragenyx CEO Dr. Emil Kakkis and a leading rare disease researcher.

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Permission granted by Dr. Emil Kakkis.

When the FDA last year refused to accept the application for a new drug to treat children and adults with an ultrarare disease, researchers and pharma insiders were befuddled.

The drug — pegzilarginase from Aeglea BioTherapeutics — performed well in clinical trials for patients with arginase deficiency, a disease that causes a buildup of the amino acid arginine and can cause physical and intellectual disability in young children. The study showed that more than 90% of patients taking the drug attained normal arginine levels compared to a placebo group.

But the FDA gave pegzilarginase what's called a "refusal to file" letter, citing lack of data supporting effectiveness. The regulator

requested evidence showing the drug's arginine-lowering effect was related to the clinical benefit. No safety concerns were raised.

Aeglea, which went through several rounds of layoffs, sold the drug to Sweden's Immedica Pharma, a larger rare disease company with several products on the market. Immedica presented new data in late August showing long-term improvement in mobility for patients, a continuation of Aeglea's original study.

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So while pegzilarginase remains on the table, some rare disease experts still question the FDA's refusal to file. Dr. Emil Kakkis, CEO of the rare disease company Ultragenyx, and Dr. Stephen Cederbaum, UCLA professor emeritus and one of the world's leading voices in arginase deficiency research (and a former medical professor of Kakkis' at UCLA), wonder how the FDA's policies led to the outright rejection of a drug that showed promise in a disease with so few options.

"Over the years, we've both been working on trying to get these ultrarare diseases treated, and arginase is one of those diseases I always thought was maybe too rare," Kakkis said. "But the science was right, and it's a fundamental question: If we figure out with all our research and science how to treat someone — no matter how rare, even 20, 30, 50 people — shouldn't we have a way of getting it approved?"

‘An important stop’

Cederbaum, who’s 86, calls himself “a lifelong student of this particular disorder” — he began working with arginase deficiency and other urea cycle disorders more than half a decade ago in 1972.

Pegzilarginase isn’t exactly the light at the end of the tunnel for arginase deficiency, Cederbaum admitted — that will likely be a gene therapy — but the enzyme therapy pegzilarginase targets what he said is the source of the disease.

“There’s an emotional component to it, and it kind of closes a circle — it’s not the final circle, and it’s not the last stop on the journey,” Cederbaum said. “But it’s an important stop, like reaching a hub and knowing you have more to go.”

His attempts at enzyme therapy for arginase deficiency go back to the early 1980s when a grant application was rejected by the NIH “because they said, ‘Who would want to do enzyme therapy when gene therapy is right around the corner?’” according to Cederbaum. But when Aeglea succeeded in a clinical trial only to face more rejection 40 years later, he was crestfallen.

“They did it the right way and they got the right result, but the criteria that were established were unrealistic and couldn’t be met,” Cederbaum said.

And that’s where Kakkis has been fighting to establish new criteria for “qualified biomarkers” that could help rare disease drugs come to market with fewer hoops to jump through, the CEO said. The FDA’s evaluation process for rare disease drugs in the accelerated approval pathway doesn’t account for the science, Kakkis said.

“Most of my time dealing with the FDA is trying to explain basic biology to them — they seem to want you to recreate and reprove basic biology over and over again, and that shouldn’t be our need,”

Kakkis said. “They are smart and well-trained, but there’s a kind of ivory tower thinking that doesn’t allow them to see the big picture and to understand that their decision didn’t improve the product — it killed the product.”

For scientists who know their patients and a disease as well as Cederbaum, the FDA can be a frustrating place to present work.

“There’s no opportunity for presenting nuance, no give and take,” Cederbaum said. “You can imagine the frustration of these patients, like Tantalus, and the grapes are just out of reach.”

Qualified biomarkers

Kakkis isn’t new to this battle. He left the industry in 2009 to form the EveryLife Foundation for Rare Diseases to accelerate and improve the regulatory process, working with Congress and the FDA to reform policies around approval .

For Kakkis, using qualified biomarkers to anticipate clinical improvement is to address the underlying cause of disease rather than treat the symptoms — it’s the fundamental drive behind precision medicine, and he feels U.S. regulators are falling behind in making that call.

Under current FDA policy, a biomarker can be used for approval if it is reasonably likely to predict clinical benefit. But for a rare disease with no other treatments that act upon a given biomarker, the requirement becomes impossibly difficult to reach, Kakkis said.

“This kind of thinking doesn’t care about patient outcomes but is just trying to create some artificial standard and have every little thing figured out, but then they obstruct good therapies,” Kakkis said. “And companies aren’t going to have unending amounts of money to invest and answer all questions for every possible thing.”

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In some cases, the FDA has taken biomarkers into account for accelerated approval for rare diseases, Kakkis pointed out. Biogen received an approval in April of its drug Qalsody for an ultrarare form of ALS based not on clinical results — the trial's primary endpoint was not met — but on the reduction in neurofilament biomarkers that indicate the drug does what it is designed to do.

"That, to me, is forward thinking and looking at the science with a balance of thinking between how much rigor and how much flexibility is needed," Kakkis said. "But a few years ago that would have been difficult because other people would have blocked it."

In Kakkis and Cederbaum's view, using arginine as a biomarker for arginase deficiency is more straightforward than neurofilaments in ALS. Similarly, a reduction in amyloid plaques for Alzheimer's is more complicated than the reduction of arginine, but it has been used to approve controversial drugs like Biogen and Eisai's Aduhelm — as well as their more clinically proven drug Leqembi.

"The problem we're seeing here is that if you're a larger rare disease or a larger market there seems to be more accommodation that's happening than for the ultrarare," Kakkis said. "I think the opposite should be true."

Refusal to file

The refusal to file distinction for a drug application is rare and often comes down to missing information — according to an FDA report finding there were 103 such rejections from 2008 to 2017. Only about 4% of new drug applications received the refusal letter during that time.

The authors of the report wrote that the agency needs to improve transparency, which it had acknowledged in 2010 but hadn't implemented as of 2021. Transparency would "help applicants avoid [refuse to file] letters and thereby facilitate timelier patient access to new therapies," the authors wrote.

Kakkis said it's possible that the regulatory process for pegzilarginase wasn't handled correctly by the company, but that shouldn't be the reason a drug that works for patients doesn't make it to the finish line.

"If the science is right, it shouldn't be just people who are savvy in how to handle regulators who get to win," Kakkis said.

Pegzilarginase is currently under regulatory review in Europe, and Immedica is discussing a path forward with the FDA. But the FDA policies Kakkis and Cederbaum hope to change could have a lasting impact larger than one rare disease.

"If we can have an impact on this, there could be about 20 treatments for ultrarare diseases that could come forward the next year, and that could change the future for all time for people with these diseases," Kakkis said.