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US FDA's Confidence In Gene Editing Safety Growing Enough That Regulatory Bar May Be Lowered

by Derrick Gingery

Some worries about heritable genetic modifications are subsiding and Center for Biologics Evaluation and Research Director Peter Marks said sponsors should consider the US for regulatory advice and clinical trials in the space.

The US Food and Drug Administration's growing comfort with gene editing has sparked a more relaxed regulatory approach to the products.

Gene editing is a concerning subject for the FDA because the products could unknowingly cause heritable genetic modifications that harm patients. At first, the agency set high safety standards for gene editing trials to proceed in the US.

Center for Biologics Evaluation and Research Director Peter Marks admitted that the bar may have been set too high initially for some gene editing products. But he said that sponsors now should feel more comfortable discussing development plans with the FDA.

"We may adjust the bar a little bit," Marks told the *Pink Sheet* on 16 October. "We would like to recalibrate and for people to know that we're open to consideration and you don't have to go to another regulator."

Heritable Genetic Modification Debate May Ignite Again As Technology Advances

By Derrick Gingery

30 Oct 2023

The change in thinking occurred over the last six months to a year, Marks said following a session at the National Organization for Rare Disorders' Breakthrough Summit.

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"We're moving so fast here," he said. "This is a fast pace for a regulator."

The adjustment is not surprising given the continued growth of gene therapy development. CBER has approved 15 products, including several over the last two years, with many more in various development stages.

CBER Director Peter Marks said the US may have to consider whether to maintain its ban on the practice of creating embryos to include heritable genetic modifications if other countries allow the practice.

Read the full article here

Vertex Pharmaceuticals Incorporated's gene therapy candidate for sickle cell disease, exa-cel, appears on track to become the first gene editing gene therapy approved by the FDA. The Cellular, Tissue and Gene Therapies Advisory Committee decided 31 October that Vertex's nonclinical analyses of potential off-target effects were sufficient. (Also see "*Vertex's Exa-Cel: Off-Target Gene Editing Analyses Sufficient Given Robust Clinical Efficacy, FDA Panel Says*" - Pink Sheet, 31 Oct, 2023.)

Making A US Sales Pitch

Marks said during the NORD conference session that New Zealand and Australia have become sites for some of the first in vivo gene editing trials and partially blamed US safety worries for more trials not being conducted in the US.

"We want to make sure that it's not something that's likely to happen," he said. "As long as we can get to there, I think that will help us get to allowing these to proceed."

In what seemed like a sales pitch to sponsors, Marks also reminded the audience that the FDA has a wealth of expertise in gene editing that can be useful as clinical trials are planned, even if they are not conducted in the US.

"We do have tremendous experience at FDA with gene therapies and genome editing, and I think it's helpful to sometimes have the information that we can provide sponsors," he said. "Obviously, I'd like to try to encourage them to be working with us."

"Not that I care so much where the trial is conducted, but that I care with whose regulatory advice it's conducted with," Marks added. "The last thing I think we want to see with rare disease patients are people treated where that data that they're treated under, or protocol, does not serve the purpose of moving towards availability of the product, that is, it won't serve a regulatory purpose. Hopefully we'll get the balance right."

Gene editing products that purposely create or modify human embryos with heritable genetic mutations cannot be accepted for review by the FDA. But Marks indicated the debate may reopen

with more countries getting into that portion of the sector. (*See sidebar*.)

Safety, Review Pathway Issues Still Linger

Even as the FDA increases its confidence with gene therapy and gene editing, challenges remain, including with product safety.

The FDA wants sponsors to monitor patients for up to 15 years after treatment to ensure long-term patient safety and efficacy. Agency officials continue to debate how best to ensure the necessary data is collected despite the many unknowns that could disrupt those plans. (Also see "*US FDA Struggling With Long-Term Follow-Up Requirements For Gene Therapies*" - Pink Sheet, 18 Oct, 2023.)

Gene therapy manufacturing also remains an issue as sponsors sometimes struggle to scale up from clinical trial to commercial operations. Marks is among those pushing for manufacturing improvements, including automated techniques. (Also see "*FDA's Marks Sees 'Two Or Three Year Window' To Transform Gene Therapy Environment*" - Pink Sheet, 11 Apr, 2023.)

In addition, the FDA wants to make the accelerated approval pathway more widely available for gene therapies, especially in the rare disease space, to speed their development. (Also see "*FDA Gene Therapy Office Chief Prefers Flexibility With Accelerated Approval Confirmatory Trials*" - Pink Sheet, 23 Sep, 2023.)

Top-line confirmatory trial data was recently announced for a high-profile product to use the pathway, *Sarepta Therapeutics, Inc.*'s Elevidys (delandistrogene moxeparvovec-rokl). The study missed the primary endpoint, but the company touted secondary endpoint data, which could complicate the decision on its application seeking a label expansion. (Also see "*Elevidys And The EMBARK Trial: Is Another Advisory Committee Meeting Coming?*" - Pink Sheet, 31 Oct, 2023.)