CAPITOL STREET

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Ultra Rare Pathway From FDA

FDA Has Authority; Congress May Not Be Needed

Relevant Companies

Our Take & Next Up

Brand new FDA Commissioner Marty Makary, MD & MPH, announces his intention to provide leniency in ultra-rare disease approvals with a new pathway. On Friday April 18, the new FDA Commissioner announced his intention to create an ultra-rare disease pathway on the Megyn Kelly show (here). We view (1) inclusion in the next User Fee authorization (2027) which renews industry fees every 5 years as a possibility but (2) the FDA likely has the authority to make these changes on its own. We note that the Rare Disease Hub continues at the FDA but has limited staffing and funding. Below see our take on the path forward, incorporating industry and patient groups (Ultragenyx, EveryLife) along with former FDA leader Janet Woodcock's ideas, over the next 1-2 years. We have said that Dr. Makary is a fan of innovation and new technologies e.g., gene editing, cell therapy and others that address an unmet need.

Key Points

We believe that the FDA likely can approve ultra-rare therapies *without* a new legislative pathway.

- Dr. Makary discussed with Megyn Kelly finding plausible mechanisms for implementation, with customized pathways & conditional approvals for ultra-rare conditions that have “75 patients in the world."
- A non randomized controlled clinical trial (CT) would be allowed, and all participants would be monitored to make inferences as soon as the data speaks, with signals. Typically, the CT is coupled with a robust post approval data generation process & requirements to update FDA on a periodic basis.
- Ultra-rare conditions often lack the developed science around endpoints. As a result, the agency could allow for additional flexibility around endpoints including the use of surrogate or novel endpoints (as seen in the accelerated approval pathway).

The ideas discussed by Commissioner Makary remind us of Ultragenyx’s proposed rare disease pathway. Ultragenyx and **EveryLife Foundation for Rare Diseases** have previously called for an ultra-rare disease pathway which allows for a distinct criteria for ultra-rare diseases. However, the agency has resisted the push to create a designation in the past. Instead, the FDA allowed for regulatory flexibility for certain ultra-rare applications which may have contributed to undermining confidence in the FDA’s regulatory decisions.

The Rare Disease Hub @ FDA appears to be going nowhere soon, but it may be revived to serve the new commitments articulated Friday. The Hub provides another opportunity to discuss the needs and challenges for ultra-rare conditions and we could see some internal FDA champions for addressing ultra-rare conditions. We note that the Rare Disease Hub lost only one member to the RIFs and continues to work on implementation of their programs. All Hub staff are currently CBER and CDER full-time employees whose work for the Hub is in addition to other duties.

What is the FDA Rare Disease Hub? Similar to the Oncology Center of Excellence (OCE), the Hub, announced in July 2024, aims to improve and accelerate rare disease therapeutic reviews through increased collaboration between the FDA divisions and stakeholders. The Hub would have three primary functions:

- Serve as a single point of connection and engagement with the rare disease community, including patient and caregiver groups, trade organizations, and scientific/academic organizations, for matters that intersect CDER/CBER.
- Enhance intercenter collaboration to address common scientific, clinical and policy issues related to rare disease product development. This would include relevant cross-disciplinary approaches related to product review and promote consistency across offices and Centers.
- Advance regulatory science with dedicated workstreams for consideration of novel endpoints, biomarker development and assays, innovative trial design, real world evidence, and statistical methods.

Former FDA leader Janet Woodcock has also been vocally supportive of an ultra rare pathway (2024), through the Haystack Project. Woodcock argues that patients with ultra-rare diseases should not have to ever receive a placebo. She notes that the double blinded placebo controlled trial gold standard should not be the only way to approve therapies for unmet needs in tiny patient populations. A new mandated pathway "would unlock investment in ultra-rare diseases, make regulatory decisions less contentious, and ensure that the bar remains high for drugs that can be evaluated using traditional methods".

Ipsita Smolinski
Managing Director I Capitol Street
ipsita@capitol-street.com

202.250.3741 I www.capitol-street.com

900 19th St NW 6th Fl
Washington, D.C. 20006

CAPITOL STREET
