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Accelerated Approval Guide Lacks Rare Disease Flexibility, Advocate Says

Recent FDA guidance on expedited drug development touches on some themes espoused by an advocate-driven white paper, but should do more to provide flexibility in allowing orphan drug developers access to the accelerated approval pathway, a rare disease advocate said. The EveryLife Foundation for Rare Diseases released a white paper hoping to influence and build on key guidance from FDA, with both documents released last week.

Throughout debate around the FDA Safety and Innovation Act, the foundation advocated for language that would facilitate orphan drug access to the accelerated approval pathway. It specifically cited challenges in qualifying biomarkers for ultra rare diseases. The foundation contends there are fewer than 300 approved treatments for nearly 7,000 rare diseases and better access to accelerated approval would increase investment in these therapies.

Congress directed FDA to consider unique issues associated with very rare diseases in writing guidance unveiled last week. The guidance outlines criteria, submission requirements, features and other details regarding fast track, breakthrough, accelerated approval and priority review programs.

"It's a good guidance to have that covers the big picture," said Emil Kakkis, president of the foundation. The guidance includes some elements that he and others in the rare disease community have been discussing such as understanding the drug's effect and the underlying disease. It also reiterates FDASIA's assertion that disease rarity is a consideration when making a determination on a surrogate endpoint.

"I think it's a good step forward," he said. "I think it will help, but I do think it could be better." He noted that the guidance has less detail than proposed in the separate white paper. The final guidance could be fleshed out with more detail directing orphan drug developers how to qualify biomarkers without basing the determination solely on clinical outcomes data, which is difficult to obtain in cases of ultra rare diseases, he said.

He particularly took issue with a section of the guidance that he said appeared at odds with intent of FDASIA, by saying clinical data is required to prove an endpoint is likely to predict clinical benefit.

"The empirical evidence may include 'epidemiological, pathophysiological, therapeutic, pharmacologic, or other evidence developed using biomarkers, for example, or other scientific methods or tools.' Evidence of pharmacologic activity alone is not sufficient, however," the guidance says. "Clinical data should be provided to support the assertion that a relationship of the surrogate or intermediate clinical endpoint to the outcome is reasonably likely, and should be relevant to the relationship between the specific endpoint to be used and the specific intended clinical benefit of the drug."

In developing the white paper, Kakkis sought feedback from FDA and other rare disease stakeholders to provide a scientific framework for the use of rare disease biomarkers in accessing accelerated approval. He said he hopes the detail in the final guidance falls somewhere between the proposed guidance document and the white paper.

The paper, titled "Accelerated Approval for Rare Diseases: Recommendations on Guidance for Industry for Qualifying Biomarkers as Primary Endpoints in Pivotal Clinical Studies," recommends pathophysiologic and pharmacologic considerations to support confidence in a biomarker's predictive value. Suggestions include disease considerations, such as whether the cause of the disease is clearly understood; drug considerations, such as when the mechanism of action is known; biomarker considerations, such as whether it has a direct relationship to an important disease cause; and preclinical considerations, such as when preclinical studies show a meaningful effect on the disease.

"It should be noted that while these considerations are not absolute requirements, they should be viewed as data points to support the use of a biomarker for (accelerated approval) in that specific context of use." The paper also recommends discussing biomarkers with FDA during the pre-investigational new drug stage to help drive investment in rare diseases earlier in the development process.

While FDA did not provide feedback directly on the document, agency officials participated in workshops discussing the white paper, Kakkis said. A section was added to the paper detailing drugs for rare diseases that had been approved based on a biomarker, with most coming through the traditional approval process, rather than accelerated approval. Kakkis said the paper was modified to convey a more rigorous scientific process, addressing FDA concerns that the white paper authors were advocating accelerated approval for rare diseases without any constraints. — *Alaina Busch* (*abusch@iwpnews.com*)