HAYSTACK PROJECT
The Voices of Ultra Rare

Need for Internal FDA Oversight of Accelerated Approval for Rare Disorders

Today. There are approximately 7,000 rare diseases, the majority of which have no FDA-approved treatments and for which there is no expectation FDA can maintain true internal expertise. Rare diseases run the gamut across the full range of organ systems, often impacting multiple organ systems, so review of rare and ultra-rare applications does not consistently fall to any one review division. Although some are reviewed by the rare disease division at FDA, many also fall to the division charged with a certain body part/system"

Problem. There is no consistency in understanding rare and especially ultra-rare dynamics, including benefit-risk assessment, lack of natural histories, and importantly, lack of established proxies or surrogate endpoints for clinical benefit. Unlike the oncology division s consistent use of progression free survival as a surrogate endpoint in accelerated approvals, other divisions rarely have such the luxury of such a well-established surrogate, in large part because the various ultra-rare diseases are not similar enough to rely on the same surrogate. Other divisions also have far less experience in applying the reasonable likely standard Congress devised for use of this pathway. This has resulted in a lack of predictability and transparency in the application of the accelerated approval pathway in rare and especially ultra-rare diseases.

Just recently, Dr. Richard Pazdur, FDA Oncology Center of Excellence director, said the accelerated approval pathway is complicated for even FDA staff to use it well. There are so many nuances. And *even within our own organization, unless you re using this on a daily basis, many people trip up on how to apply it."* Rare disease patients, and the researchers and sponsors they partner with, should not be subject to a lottery" of being assigned a review division that may or may not understand how to apply this pathway when each day that passes is so critical in the life of a patient suffering from a debilitating and ever-worsening rare disease.

Solution. A multi-prong approach is needed to quickly and efficiently improve the predictability with use of a very important tool for rare disease patients:

a. **Cross-Center Collaboration**. It is clear that some divisions have far more experience with the accelerated approval pathway than others. Regular meetings, educational sessions, etc. with the Oncology division, for example, should be required for cross collaboration and deepening understanding of how to apply the pathway. These learning should include how to identify a surrogate, how to consider data related to the surrogate, trends that suggest the need to support, refine, or eliminate the surrogate, and how to make defensible judgements about the 'reasonably likely' standard.

b. **Reasonably Likely/Confirmatory Trials.** Cross center collaboration should also specifically include working closely with the Office of Pediatric Therapeutics where applicable. With over 70% of rare and ultra-rare diseases affecting children, it is critical that all review divisions continue to improve their understanding of child development milestones and the disease mechanisms disrupting them. This is critical to enabling reviewers to understand that, for example, they cannot expect a child to gain the ability to walk as a result of a treatment before

'testing' the child's loss of the function. To put it simply, these patients are not fully grown adults for whom comparison of function is simple.

c. **Oversight.** CDER's Office of New Drugs must dedicate staff to review use of the accelerated pathway, or lack thereof, by review division. Staff should document when a request from a sponsor has been received for consideration of a surrogate endpoint, the Division's decision, as well as the basis for the decision. Where an outright decision is not made, but direction provided to the sponsor (e.g., initial recommendation or support for data collection to support a surrogate endpoint), and then subsequently that determination, support or recommendation is withdrawn, oversight staff should require documentation of a clear evidentiary basis for such a reversal/conclusion that the endpoint is not 'reasonably likely' to be associated with a clinical benefit.

   Such oversight should also include the lack of use of the Accelerated Pathway, so oversight staff can query lack of use.

   This should aid the agency in identifying internal staff needs and dedicate resources accordingly, and to use the pathway and surrogate endpoints consistently, with the understanding that FDA must work with limited knowledge and understanding of ultra-rare conditions, and the need to tailor benefit-risk thresholds to accommodate conditions that are of an aggressively degenerative nature and/or have no available treatment options or proven surrogate endpoints.

   Staff should document when a request

d. **Meeting and Guidance.** FDA should conduct a series of small group meetings with multiple stakeholders to collect input and issue guidance on:

   (i) how to use their flexibilities in the case of ultra-rare diseases that are multifactorial, heterogeneous, and severe when treatments establish an adequate degree of safety and efficacy with appropriate guardrails;

   (ii) how to modify benefit-risk assessments so as to make them 'fit for purpose' –
   - Rare or ultra-rare conditions
   - Safety profile of the biomarker is low
   - Burden of disease is high
   - No treatments exist
   - Significant impact on quality of life

These circumstances should be weighted accordingly in the division's assessment against the 'reasonably likely' standard, since minimal risk can also mean there is tolerance for unclear benefit. This is, after all, the call from patients that led to the creation of the Accelerate Approval pathway.

a. **At Approval.** FDA must release a statement upon approval of a treatment using the Accelerated Approval pathway about the full force and effect of this approval. FDA must clarify in this statement that the approval decision meets the full rigor applicable in all FDA

decisions on safety and efficacy, and any stakeholders relying on such approval should not in any way limit or interpret the approval to be limited in any way.

b. **Confirmatory Trials/Withdrawal.** Our patients deserve the same hope that treatments bring to more common conditions. We may have to take a more circuitous route, but we support the need to confirm clinical benefit. We also recognize confirmatory data may be more difficult to collect when there are so few patients with an ultra rare condition, however, due to the small community of patients and providers, these post-market data may actually be easier to get than for more common diseases. Regardless, we rely on FDA's review of such circumstances to assess and quickly act on the need to withdraw a treatment if, in spite of ultra-rare circumstances, data is not collected in a reasonable timeframe, as determined by the agency.

Haystack Project strongly believes in the need to preserve and protect the Accelerated Approval pathway. We are often told we cannot legislate on the basis of one or two anecdotal patient stories. And yet, we are worried that a few poor examples have rushed us into 'reforming 'a pathway when FDA already has the legal authority to make changes and improvements.

- FDA is beginning to increase its vigilance and enforcement on companies that fail to complete confirmatory studies required as a condition of marketing.
- Some sponsors are choosing to withdraw accelerated approval products rather than contend with additional agency scrutiny
- FDA is increasing its removal of products from the market

If we are to proceed with legislation, the solutions outlined above would allow our community to support earlier agency-sponsor engagement on confirmatory studies and any additional authority the agency believes is needed to remove products from the market. However, these must be married to the reforms outlined above and recognize the vastly different circumstances of ultra-rare diseases.

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