The Accelerated Approval Pathway and Rare Diseases

Accelerated Approval Overview:

- In 1992, in response to the HIV/AIDS crisis, the U.S. Food and Drug Administration (FDA) instituted the Accelerated Approval pathway to improve the time to approve drugs that treat serious conditions that fill an unmet medical need based on substantial evidence of safety and efficacy and a surrogate endpoint* that is reasonably likely to predict outcomes like irreversible mortality or morbidity.[1]
- By 1996, antiretroviral drugs approved under the Accelerated Approval pathway helped transform HIV/AIDS from a fatal disease into a manageable chronic illness. Since 1992, 278 drugs have been approved under the Accelerated Approval pathway with nearly 50% going on to traditional approval.
- In 2012, the Food and Drug Administration Safety Innovations Act (FDASIA) was passed by Congress. FDASIA amended the Food, Drug, and Cosmetic Act to allow surrogate or intermediate clinical endpoints to be used in Accelerated Approval trials.
- Accelerated Approval is NOT the same as the Conditional Approval pathway in the E.U. Conditional approvals may use a clinical endpoint and must be renewed annually based on satisfactory progress in demonstrating the treatment's effectiveness and a review of safety issues.

Importance for Rare Disease Patients:

- 95% of the more than 10,000 known rare diseases have no FDA-approved therapy.
- The development timeline from pre-clinical studies to FDA approval for a rare disease drug takes an average of 15 years.
- In clinical trials, endpoints are used to determine whether the investigative therapy has a clinically meaningful benefit for patients. Endpoints include survival, functional capacity (i.e., years ventilator-free), and/or development of new or worsening disease symptoms.[2]
- Proving that a drug has clinical benefit, which is required for traditional approval, can be challenging due to:
  - Small number of patients available for clinical trials
  - Variability in disease presentation among patients
  - Slow/varied progression of some diseases
  - Multiple organ impact

MYTH vs FACT

MYTH	FACT
The accelerated approval pathway is not as rigorous as traditional approval.	Accelerated approval is NOT a lower standard. Treatments approved via the AA pathway are subject to the same statutory standards for proving safety and efficacy as traditional drug approvals.
Surrogate endpoints are inferior to clinical outcome measures.	Surrogate endpoints can have advantages over clinical outcomes, especially in cases where they can more accurately capture real-time disease progression or improvement.

Surrogate endpoints:

- Are markers of expected benefit of the drug. These can include enzyme levels, physical changes, radiologic imaging, or other relevant measures.
- Are not direct markers of clinical benefit but are intermediate signs of an expected and/or likely benefit to patients.
- Allow for shorter clinical trials and thus substantially shorten the length of time to FDA approval.

EveryLife Foundation for Rare Diseases

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Examples of surrogate endpoints used in accelerated approval trials

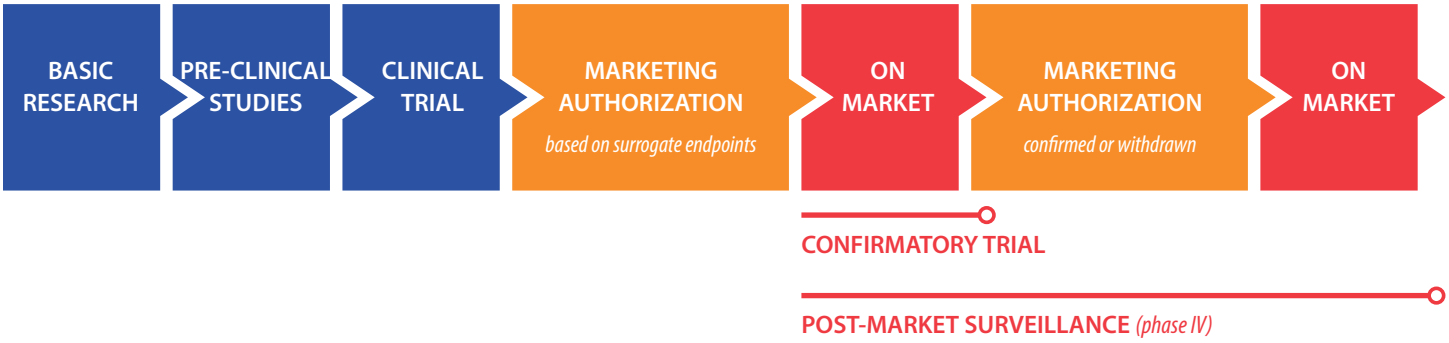
	SURROGATE ENDPOINT	EXPECTED CLINICAL BENEFIT	EXPLANATION
Oncology	Tumor shrinkage	Decreased mortality	While tumor shrinkage is not a direct measurement of improved survival, it is reasonably likely that tumor shrinkage may improve the course of disease and evolve standard of care.
Gene Therapy	Increased protein production	Improved function of downstream tissues	Restoring partial gene function through gene therapy allows for a more-functional protein to be produced. Increased protein production has been shown to slow or stabilize disease progression.
Rare Disease *Ex. enzyme deficiencies*	Enzyme substrate presence	Avoidance of organ failure	Enzyme replacement therapy (ERT) is designed to restore the body's ability to breakdown the target substrates. Measuring these substrates is an indication that the ERT is working as expected but is not a direct measure of improved outcomes such as avoiding renal or other organ failure.

Accelerated Approval Process:

Application – standard 10-month review (unless expedited by a fast track/priority review designation) for efficacy, effectiveness, and safety.

Approval – FDA grants accelerated approval with specified timeline for required confirmatory trial(s) and post-market surveillance.

Post-accelerated approval – confirmatory studies (called "phase 4 confirmatory trials") conducted. From here, the FDA can convert the accelerated approval to a full, traditional approval if the drug confirms clinical benefit. If no clinical benefit is shown, the FDA has the regulatory authority to remove the drug from the market.



References:

[1] https://www.fda.gov/patients/fast-track-breakthrough-therapy-accelerated-approval-priority-review/accelerated-approval

[2] https://www.fda.gov/media/84987/download

About the EveryLife Foundation

The EveryLife Foundation for Rare Diseases is a 501(c)(3) nonprofit, nonpartisan organization dedicated to empowering the rare disease patient community to advocate for impactful, science-driven legislation and policy that advances the equitable development of and access to lifesaving diagnoses, treatments and cures.

everylifefoundation.org

About the Partnership to Fight Chronic Disease (PFCD)

The Partnership to Fight Chronic Disease (PFCD) is an internationally-recognized organization of patients, providers, community organizations, business and labor groups, and health policy experts committed to raising awareness of the number one cause of death, disability, and rising health care costs: chronic disease.

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