U.S. FOOD & DRUG ADMINISTRATION

Rare Disease Drug Development

Emily R. Freilich, MD
Director
Division of Neurology 1 / Office of Neuroscience
Center for Drug Evaluation and Research

February 7, 2024
National Academies of Sciences, Engineering, and Medicine

Regulatory Standards for Effectiveness

- *Substantial evidence of effectiveness* is the legal standard to establish the effectiveness of a drug for approval
  - Refers to both quantity and quality of the data

- *Substantial evidence* is defined in section 505(d) of the Food, Drug and Cosmetic Act as "evidence consisting of adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved, on the basis of which it could fairly and responsibly be concluded by such experts that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling or proposed labeling thereof"

Source: 2019 Draft Guidance: *Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products* https://www.fda.gov/media/133660/download

Examples of how FDA considers flexibility when advising and evaluating drug development programs

- **2019 Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products (draft guidance)–**
  - **One Adequate and Well-controlled investigation and confirmatory evidence**: "If [FDA] determines, based on relevant science, that data from one adequate and well-controlled clinical investigation and confirmatory evidence (obtained prior to or after such investigation) are sufficient to establish effectiveness, [FDA] may consider such data and evidence to constitute substantial evidence."
    - 2023 DRAFT GUIDANCE ***Demonstrating Substantial Evidence of Effectiveness With One Adequate and Well-Controlled Clinical Investigation and Confirmatory Evidence***
  - **Reasonably likely surrogate endpoints:** "the accelerated approval regulations… acknowledg[e] that reliance on a surrogate endpoint "almost always introduces some uncertainty into the risk/benefit assessment, because clinical benefit is not measured directly and the quantitative relation of the effect on the surrogate to the clinical effect is rarely known.""
  - **Statistical considerations:** -- "For a serious disease with no available therapy or a rare disease where sample size might be limited, as discussed further below, a somewhat higher p value – if prespecified and appropriately justified – might be acceptable."
- **2023 Rare Diseases: Considerations for the Development of Drugs and Biological Products**
  - **Nonclinical studies** – "For products being developed for severely debilitating or life-threatening rare disease indications, clinical investigations can often proceed with modifications to the typical nonclinical development programs described in guidance. "

CDER Neurology Approvals for Rare Diseases in 2023

- Omaveloxolone (Skyclarys)
- Trofinetide (Daybue)
- Tofersen (Qalsody)**
- Rozanolixizumab-noli (Rystiggo)
- Zilucoplan (Zilbrysq)
- Vamorolone (Agamree)
- Eplontersen (Wainua)

** accelerated approval

CDER Neurology Approvals for Rare Diseases in 2023

- **Omaveloxolone (Skyclarys)**
  - First approved treatment for Friedreich's ataxia (FA), a rare inherited degenerative disease that damages the nervous system, characterized by impaired coordination and walking
  - Approved through one adequate and well controlled study plus confirmatory evidence
- **Trofinetide (Daybue)**
  - First approved treatment for Rett syndrome, a rare genetic disease characterized by profound neurological impairment, developmental regression, epilepsy, impaired communication, and related respiratory and GI complications
  - Approved through one adequate and well controlled study plus confirmatory evidence
- **Tofersen (Qalsody) (accelerated approval)**
  - First targeted therapy approved to treat patients with ALS associated with a mutation in the superoxide dismutase 1 (SOD1) gene (SOD1-ALS)
  - Antisense oligonucleotide that targets SOD1 mRNA to reduce the synthesis of SOD1 protein
  - Approved via accelerated approval based on a reduction in plasma neurofilament light (NfL), a blood-based biomarker of axonal injury and neurodegeneration found to be reasonably likely to predict clinical benefit in patients with SOD1-ALS, in the context of concurrent evidence of target engagement demonstrated by a reduction in SOD1 protein


FDA
U.S. FOOD & DRUG
ADMINISTRATION