Designing drug development programs to meet the standards needed to constitute confirmatory evidence in support of a single positive adequate and well-controlled study in neuroscience

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Disclosures

- I am an attorney and full-time employee of Hyman, Phelps & McNamara, P.C., a law firm focused on FDA-regulated products and industry.
- I have no financial interests in any of the products mentioned in this presentation, nor in any of its competitors.
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Evolution of FDA Statutory Authority

- **1938** – New drug approval based on safety only
- **1962** – Efficacy added to the FDA approval authority
- **1997** – Standard for efficacy clarified to make single study plus confirmatory evidence pathway explicit
- **Present** – FDA interpretation and application of this pathway is illuminating what constitutes confirmatory evidence

Substantial Evidence of Effectiveness

1962 – Kefauver-Harris Amendments

- FDA may deny an application if "there is a lack of **substantial evidence** that the drug will have the effect it purports or is represented to have . . . ."
- "[T]he term "substantial evidence" means evidence consisting of **adequate and well-controlled investigations, including clinical investigations** . . . ."

1997 – Food and Drug Administration Modernization Act

- "If the Secretary 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, the Secretary may consider such data and evidence to constitute substantial evidence…."

Confirmation or Substantiation?

- Traditional view of substantial evidence of effectiveness = two adequate and well-controlled (AWC) clinical trials
- 2nd trial → assurance that 1st trial's results are not chance finding
- Confirmatory evidence = alternative means of assurance
- Confirmatory evidence replaces the 2nd trial as the means of *substantiating* the 1st trial

A Few Confirmatory Evidence Approvals

Zilbrysq (CDER, 2023)

- C5 complement inhibitor for generalized myasthenia gravis (gMG) in AChR antibody positive patients
- Primary – MG-ADL at 12 weeks (strong support from secondary endpoint QMG score)
- Confirmatory – **mechanistic PD marker** (C5 levels)

Wainua (CDER, 2023)

- ASO (GalNAc conjugate) for hereditary transthyretin amyloidosis polyneuropathy (hATTR-PN)
- Primary – mNIS+7 at 35 weeks (strong support from secondary endpoint Norfolk QoL-DN)
- Confirmatory – **mechanistic PD marker** (serum TTR) and knowledge from **other approved drugs in the same class**

Lenmeldy (CBER, 2024)

- Ex vivo gene therapy (CD34+ HSC transduced with LVV for arylsulfatase A gene) for metachromatic leukodystrophy (MLD)
- Primary – motor and neurocognitive severe motor impairment free survival (pooled single arm studies compared to natural history)
- Confirmatory **– mechanism of action**, **pre-clinical** data, and **clinical biomarkers** (ARSA enzyme and brain MRIs)

Kebilidi (CBER, 2024)

- CNS administered AAV-gene therapy for aromatic L-amino acid decarboxylase deficiency (AADC)
- Primary – major motor milestone at 48 weeks compared to natural history
- Confirmatory – **mechanistic PD markers** (CSF HVA and putamen specific ^{18}F-DOPA uptake)

Relevance of this Confirmatory Evidence Pathway

Crucial for rare disease drug development but applies to *both* prevalent conditions and rare diseases

- Accelerate development within and across development programs
- Potential to maximize the value of data gathered early in development and in precompetitive spaces
- Natural History, early phase, nonclinical data on a drug's effects could even be leveraged to support approval