Recent Drug Approvals in the Office of Neuroscience at CDER: Lessons Learned

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Disclaimer: Views expressed in this presentation are those of the speaker and do not necessarily represent an official FDA position

Drug development challenges in neuroscience

- Lack of understanding of disease pathophysiology
- Diseases defined by phenotype/syndrome rather than biology
- Disease heterogeneity (genotype and phenotype)
- Clinical outcome assessments appropriate for regulatory use often lacking
- Neurodegenerative diseases are often slowly progressive; pathology may develop years before symptom onset
- Delivery across blood-brain barrier
- Many are rare diseases

CDER Recent Notable Neuroscience Approvals

- **Schizophrenia**
  - COBENFY (xanomeline and trospium chloride); 2024
- **Post-partum depression**
  - ZURZUVAE (zuranolone); 2023
  - ZULRESSO (brexanolone); 2022
- **ALS with superoxide dismutase 1 (SOD1) gene mutation**
  - QALSODY (tofersen); 2023*
  - RELYVRIO (sodium phenylbutyrate and taurursodiol); 2022
- **Alzheimer's disease**
  - ADUHELM (aducanumab); 2021*
  - LEQEMBI (lecanemab); 2023
  - KISUNLA (donanemab); 2024
- **Friedreich's ataxia**
  - SKYCLARYS (omaveloxolone); 2023
- **Rett Syndrome**
  - DAYBUE (trofinetide); 2023
- **Duchenne muscular dystrophy**
  - AGAMREE (vamorolone); 2023
  - DUVYZAT (givinostat); 2024
- **Myasthenia Gravis**
  - VYVGART (efgartigmod); 2021
  - RYSTIGGO(rozanolixizumab); 2023
  - ZILBRYSQ (zilucoplan); 2023
- **Seizures**
  - ZTALMY (ganaxolone), CDKL5 deficiency; 2022
  - FINTEPLA (fenfluramine), Dravet syndrome; 2022
- **Multiple Sclerosis**
  - TYRUKO (natalizumab biosimilar); 2023

*accelerated approval

Approval pathways

- Approval (i.e., Traditional, Standard, Full)
  - Substantial evidence of effectiveness demonstrated on a **direct measure of clinical benefit** (e.g., how a patient feels, functions, or survives) or validated surrogate
- Accelerated Approval
  - Substantial evidence of effectiveness demonstrated on an **endpoint that is not itself a direct measure of the clinical benefit of interest but is instead reasonably likely to predict that clinical benefit** (e.g., surrogate or intermediate clinical endpoint)
  - Serious or life-threatening diseases with an unmet need
  - Subsequent confirmation of clinical benefit is typically required

- Drug is safe for use under the conditions prescribed, recommended, or suggested in the proposed labeling

Regulatory standards for effectiveness

- **Substantial evidence of effectiveness (SEE)**
  - Legal standard to establish the effectiveness of a drug for approval
  - Required for all diseases, regardless of seriousness of the disease or availability of other therapies
  - *"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"*

Section 505(d) of the Food, Drug and Cosmetic Act

Substantial evidence of effectiveness (SEE)

- Independent substantiation of favorable results
  - Reduces the possibility that a chance occurrence in a single study will lead to an erroneous conclusion that a treatment is effective
- Pathways to SEE
  - Two adequate and well-controlled (AWC) studies, each convincing on its own
  - Single AWC study alone that functions as two independent studies
  - Single AWC study plus confirmatory evidence (CE), considers:
    - Seriousness of the disease and unmet need
    - Persuasiveness of the single study and robustness of the confirmatory evidence
    - Feasibility of conducting more than one adequate and well-controlled study

Regulatory Themes

- Confirmatory Evidence
- Biomarkers
- Clinical Outcome Assessments (COA)
- Real World Evidence (RWE)
- Model Informed Drug Development (MIDD)
- Patient Focused Drug Development (PFDD)

Schizophrenia

- Xanomeline and trospium chloride; Approval September 2024
  - Xanomeline is a muscarinic acetylcholine receptor agonist in the central nervous system; not previously approved
  - Trospium chloride a muscarinic antagonist in the peripheral tissues approved for the treatment of overactive bladder
- Approved based on two adequate and well-controlled studies

Alzheimer's Disease

- Monoclonal antibodies directed toward amyloid-beta
- Accelerated approval for aducanumab (2021), lecanemab (2023)
  - Surrogate endpoint (SE): Reduction of amyloid plaque burden on amyloid PET imaging
- Traditional approval for lecanemab (2023) and donanemab (2024)
  - Slowing of decline on multiple clinical outcome assessments
- Benefit-Risk Assessment
  - Seriousness of disease
  - Meaningfulness of results
  - Ability to manage risk (e.g., amyloid-related imaging abnormalities, intracerebral hemorrhage)

SOD1 ALS

- Tofersen for ALS with superoxide dismutase 1 (SOD1) gene mutation; Accelerated Approval March 2023
- Intrathecal ASO that binds to SOD1 mRNA
- SEE: Single AWC study with CE
  - AWC: negative primary clinical endpoint; nominally significant but large and robust reduction in plasma neurofilament light chain (NfL), a marker of neuronal degeneration, found to be a SE reasonably likely to predict benefit
  - CE: SOD1 protein reduction provides support for mechanism of drug
- Study to confirm and verify clinical benefit is underway

ALS (sporadic)

- Sodium phenylbutyrate and taurursodiol approval for amyotrophic lateral sclerosis (ALS); September 2022
- SEE: Single AWC study with CE
  - AWC: positive results on pre-specified analysis of ALSFRS-R, not robust
  - CE: Post hoc long-term analyses of overall survival
- Subsequent Phase 3 study was negative in March 2024; marketing stopped

Rett Syndrome

- Trofinetide approval for Rett syndrome; March 2023
- SEE: Single AWC study with CE
  - Co-primary endpoints: Rett Syndrome Behavioral Questionnaire (RSBQ) and Clinical Global Impression of Improvement
- Confirmatory evidence
  - Supported by data from Phase 2 study demonstrating positive results on the same endpoints and exposure-response analyses

Other examples of CE

- Omaveloxolone for Friedreich's ataxia; February 2023
- Givinostat approval for Duchenne muscular dystrophy; March 2024
- CE based on:
  - Use of real-world evidence from natural history studies
  - Biomarker data that provides pharmacodynamic mechanistic support

Take Home Points

- SEE required for both traditional and accelerated approval
  - Approach for achieving SEE will depend on the disease and study results
  - Consider plan for establishing SEE and clinical benefit early in development program
- Drug development tools (e.g., biomarkers, COAs, MIDD) can be leveraged for more efficient development
  - Quality data and strong scientific rationale are critical
- RWE can contribute to confirmatory evidence
  - Pre-specification of analyses provides the most interpretable data
- Patient/caregiver input is informative for drug development and regulatory decision-making
  - Design of trials
  - Benefit-Risk Assessment


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