COMMITTEE ON
ENERGY & COMMERCE
CHAIRMAN FRANK PALLONE, JR.

MEMORANDUM

July 27, 2021

To: Subcommittee on Health Members and Staff

Fr: Committee on Energy and Commerce Staff

Re: Hearing on "The Path Forward: Advancing Treatments and Cures for Neurodegenerative Diseases."

On **Thursday, July 29, 2021, at 11 a.m. (EDT), in the John D. Dingell Room, 2123 of the Rayburn House Office Building, as well as remotely via Cisco WebEx online video conferencing**, the Subcommittee on Health will hold a legislative hearing entitled, "The Path Forward: Advancing Treatments and Cures for Neurodegenerative Diseases."

I. BACKGROUND

The brain is the most complex organ in the human body; it controls a person's senses, movement, behavior, emotion, and every other aspect of the human experience.[1] For most of history, the brain was a mystery to scientists and philosophers, but rapid advances in science and research have accelerated our understanding of how the brain functions.[2]

Although there are many illnesses and conditions that can affect the brain, neurodegenerative diseases are especially complex and debilitating. Neurodegenerative diseases involve the degradation of neurons in the brain or peripheral nervous system, ultimately resulting in the death of the neuron, which causes the brain to deteriorate over time and results in the breakdown of mobility, coordination, or cognition.[3] The most common neurodegenerative diseases are Alzheimer's disease and Parkinson's disease.[4] It is estimated that more than six million Americans are currently living with Alzheimer's disease and nearly one million with

[1] National Institute of Neurological Disorders and Stroke, *Brain Basics: Know Your Brain* (accessed July 14, 2021) (www.ninds.nih.gov/Disorders/Patient-Caregiver-Education/Know-Your-Brain#Neurological%20Disorders).

[2] *Id.*

[3] National Institute of Environmental Health Sciences, *Neurodegenerative Diseases* (accessed July 14, 2021) (www.niehs.nih.gov/research/supported/health/neurodegenerative/index.cfm).

[4] *Id.*

Parkinson's disease.[5,6] Other neurodegenerative disorders include motor neuron diseases—including amyotrophic lateral sclerosis (ALS)—Ataxia, Huntington's disease, and multiple symptom atrophy.[7] Treatments to relieve some physical and cognitive symptoms of neurodegenerative diseases exist, but there are no known cures.[8]

II. RESEARCH AND REGULATORY AGENCIES

A. National Institutes of Health Institutes and Centers

The National Institutes of Health (NIH) is a major contributor to brain and neurodegenerative disease research, coordinating and developing research through the Brain Research Through Advancing Innovative Neurotechnologies (BRAIN) Initiative.[9] The BRAIN Initiative was launched in 2013 with the goal of accelerating and developing technologies that will allow scientists to map, study, and understand the brain's complex cells and neural circuits as they function in living humans.[10] The BRAIN Initiative is coordinated by ten NIH Institutes and Centers (ICs), two of which focus specifically on aging and neurological disorders: the National Institute on Aging (NIA) and National Institutes for Neurological Disorders and Stroke (NINDS).[11] Moreover, NIA, in close collaboration with NINDS, leads the trans-NIH Alzheimer's Disease and Related Dementias program.[12] On July 19, 2021, NIH released their annual "Professional Judgement Budget for Alzheimer's Disease and Related Dementias"; the budget report estimated that an additional $226 million would be needed in fiscal year (FY) 2023

[5] Alzheimer's Association, *Facts and Figures* (accessed July 21, 2021) (www.alz.org/alzheimers-dementia/facts-figures).

[6] Parkinson's Foundation, *Statistics*, (Accessed July 14, 2021) (www.parkinson.org/Understanding-Parkinsons/Statistics).

[7] UT Southwestern Medical Center, *Neurodegenerative Disorders* (accessed July 14, 2021) (utswmed.org/conditions-treatments/neurodegenerative-disorders/).

[8] *See* note 3.

[9] National Institutes of Health, *The BRAIN Initiative* (accessed July 16, 2021) (braininitiative.nih.gov/).

[10] The White House, *About the BRAIN Initiative* (Accessed July 16, 2021) (obamawhitehouse.archives.gov/BRAIN).

[11] *Id.*

[12] National Institutes of Health, *Tran-NIH Initiatives: Congressional Justification FY 2022* (accessed July 21, 2021) (officeofbudget.od.nih.gov/pdfs/FY22/br/2022%20CJ%20Overview%20Trans-NIH%20Initiatives.pdf).

to meet the goal of effectively preventing and treating these neurodegenerative diseases by 2025.[13]

B. Food and Drug Administration

The Food and Drug Administration (FDA) is the federal regulatory agency responsible for the review and approval of drugs, biological products, and medical devices, including treatments for neurodegenerative diseases. Developers of these products and treatments typically rely on FDA's standards for safety and efficacy to guide clinical research and development of investigational therapies.

To assist developers in the clinical development of drugs and biologics to treat ALS, FDA released guidance in September 2019, which discussed the agency's thinking on development programs and clinical trial designs for treatment of ALS.[14] As part of this guidance, FDA advised that developers should communicate early with those affected by ALS to understand how patients view treatment goals and risk tolerance.[15] FDA also said that developers should not "unnecessarily exclude patients from trial enrollment based on characteristics such as age or disease stage unless scientifically justified," and suggested that even if a developer wanted to study a smaller subset of patients for a primary analysis, a broader population could be included in the trial and considered secondary and supportive.[16] FDA also discussed appropriate endpoints for judging effectiveness, which may include muscle strength, respiratory function, survival time, and mortality.[17] The guidance document also says that FDA will consider patient tolerance for risk and the serious and life-threatening nature of the condition in the context of statutory requirements for safety and efficacy.[18]

Additionally, in January 2021, the Center for Biologics Evaluation and Research (CBER) at FDA released draft guidance for industry stakeholders seeking to develop human gene therapies for neurodegenerative diseases.[19] The guidance discusses considerations for preclinical and clinical studies of gene therapies, including proof-of-concept data, functional endpoints,

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[13] National Institutes of Health, *NIH Professional Judgment Budget for Alzheimer's Disease and Related Dementias for Fiscal Year 2023* (July 19, 2021) (www.nia.nih.gov/sites/default/files/2021-07/bypass-budget-report-fy23.pdf).

[14] Food and Drug Administration, *Amyotrophic Lateral Sclerosis: Developing Drugs for Treatment Guidance for Industry* (Sept. 2019) (www.fda.gov/media/130964/download).

[15] *Id.*

[16] *Id.*

[17] *Id.*

[18] *Id.*

[19] Food and Drug Administration, *Human Gene Therapy for Neurodegenerative Diseases Draft Guidance for Industry* (accessed July 21, 2021) (www.fda.gov/regulatory-information/search-fda-guidance-documents/human-gene-therapy-neurodegenerative-diseases).

placebo-controlled study design, study populations, dose selection, safety considerations, and patient experience, among others.[20] The guidance also identifies potential expedited pathway opportunities for industry stakeholders seeking to address unmet clinical needs in life-threatening conditions, such as Alzheimer's disease and ALS.[21] These pathways may include regenerative medicine advanced therapy designation, breakthrough therapy designation, fast track designation, accelerated approval, and priority review.[22]

III. THE CLINICAL RESEARCH AND DRUG APPROVAL PROCESS IN THE UNITED STATES

A. Drug Development and Approval

After discovering a potential new drug product and conducting preclinical research to assess basic questions about a drug's safety, developers are required to conduct clinical trials to assess a drug's safety in the human body.[23] Researchers design a specific protocol, which includes who qualifies to participate (also called "selection criteria" or "inclusion and exclusion criteria"), the size and length of the study, whether there will be a control group, how the drug will be given to patients, and how data will be collected and assessed, reviewed, and analyzed.[24] Developers then submit this information, along with preclinical research data, such as animal studies and toxicity data, manufacturing information, data from prior human research, and information about the investigators, to FDA in an application for an Investigational New Drug (IND).[25]

After an IND is approved, clinical research can begin. Phase 1 clinical trials, which involve 20-100 healthy volunteers or people with the disease or condition and last several months, study the safety of the drug and appropriate dosage.[26] Phase 2 clinical trials are larger, involving several hundred people and lasting several months to two years, and provide data on efficacy and side effects which can refine research questions, develop research methods, and design protocols for a Phase 3 clinical trial.[27] In the Phase 3 trial, hundreds or thousands of

[20] *Id.*

[21] *Id.*

[22] *Id.*

[23] Food and Drug Administration, *Step 3: Clinical Research* (accessed July 23, 2021) (www.fda.gov/patients/drug-development-process/step-3-clinical-research).

[24] *Id.*

[25] *Id.*

[26] *Id.*

[27] *Id.*

volunteers with the disease or condition are studied for approximately one to four years for efficacy of the drug and for side effects and adverse reactions.[28]

At the conclusion of the clinical trial process, if a drug shows evidence of safety and efficacy, the developer may submit data, along with proposed labeling, safety updates, abuse information, patent information, data from studies conducted outside the United States, institutional review board compliance information, and directions for use, to FDA in a New Drug Application (NDA).[29] After receiving the application, FDA will review it and conduct inspections, and may consult an expert advisory committee to provide independent feedback.[30] At the conclusion of the review, FDA may approve the drug, or may communicate issues that need to be resolved before it can be approved, such as questions about existing data, or FDA may require additional studies before an approval can be granted.[31]

B. Expanded Access

The process from discovery through phase 3 clinical trials can take years, during which time those diagnosed with conditions without approved therapies, including many neurodegenerative diseases, may be left with limited treatment options. In certain situations, FDA and developers may allow certain individuals to have access to investigational therapies outside the context of a clinical trial.[32] This pathway, called "expanded access," and sometimes referred to as "compassionate use," may be appropriate when all of the following criteria are met: a patient has a serious disease or condition, or whose life is immediately threatened by their disease or condition, there is no satisfactory alternative therapy, patient enrollment in a clinical trial is not possible, the patient's physician determines potential benefit justifies the potential risk of treatment, and providing the product will not interfere with investigational trials that could support a medical product's development or marketing approval for the treatment indication.[33] To qualify for expanded access, the patient's physician can approach the company to obtain agreement that it will provide the drug, and if the developer agrees, the physician submits the request to FDA.[34] FDA has said the agency approves 99 percent of expanded access requests,

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[28] *Id.*

[29] Food and Drug Administration, *Step 4: FDA Drug Review* (accessed July 23, 2021) (www.fda.gov/patients/drug-development-process/step-4-fda-drug-review).

[30] *Id.*

[31] *Id.*

[32] Food and Drug Administration, *Expanded Access* (accessed July 23, 2021) (www.fda.gov/news-events/public-health-focus/expanded-access).

[33] *Id.*

[34] House Committee on Energy and Commerce, Subcommittee on Health, Testimony of Scott Gottlieb, M.D., Commissioner of Food and Drugs (Oct. 3, 2017) (www.fda.gov/news-events/congressional-testimony/examining-patient-access-investigational-drugs-10032017).

but does not have the power to compel a company to make a product available.[35] According to former Commissioner Scott Gottlieb, "[t]he most common obstacle to access to the investigational product is the willingness or ability of companies to provide it," and when considering a request, companies "may decline for a variety of reasons."[36]

IV. CONGRESSIONAL ACTION

Congress has made significant investments in federal neurodegenerative disease research. The 21st Century Cures Act, signed into law on December 13, 2016, authorized over $4 billion dollars to NIH for biomedical research, including over $1.5 billion for the BRAIN Initiative.[37,38] The 21st Century Cures Act also authorized $500 million to FDA to accelerate drug development, innovation, and professional recruitment.[39] Further, the law directed FDA to provide guidance on novel clinical trial designs, required drug manufacturers to post publicly their policies related to expanded access, and also established the Regenerative Medicine Advanced Therapy (RMAT) and the Breakthrough Devices programs at FDA, which aim to expedite the review of certain biological and medical device products.[40] The Food and Drug Administration Reauthorization Act (FDARA) also required FDA to issue guidance regarding eligibility for clinical trials, and in particular developing and broadening eligibility criteria, and how to apply broad eligibility criteria for clinical trials for rare diseases or conditions.[41]

V. WITNESSES

Panel I

Patrizia Cavazzoni, M.D.
Director, Center for Drug Evaluation and Research
U.S. Food and Drug Administration

Richard J. Hodes, M.D.
Director, National Institute on Aging
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[35] *Id.*

[36] *Id.*

[37] 21st Century Cures Act, Pub. L. No. 114-255.

[38] National Institutes of Health, *The 21st Century Cures Act* (accessed July 21, 2021) (www.nih.gov/research-training/medical-research-initiatives/cures).

[39] Food and Drug Administration, *21st Century Cures Act* (accessed July 21, 2021) (www.fda.gov/regulatory-information/selected-amendments-fdc-act/21st-century-cures-act).

[40] *Id.*

[41] FDA Reauthorization Act of 2017, Pub. L. No. 115-52.

Walter J. Koroshetz, M.D.
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Panel II

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