FDA Guidance on Drug Development for Early AD

On February 15, the U.S. Food and Drug Administration (FDA) announced the availability of draft guidance for industry titled "Early Alzheimer's Disease [AD]: Developing drugs for treatment." The guidance, according to documentation released by the FDA and published in the *Federal Register* on February 16, "is intended to assist sponsors in the clinical development of drugs for the treatment of the stages of sporadic AD that occur before the onset of overt dementia." The new document revises guidance for industry titled "Alzheimer's disease: Developing drugs for the treatment of early-stage disease" and issued on February 8, 2013. The public comment period opened on February 16 and will close on May 17 before preparation of a final version. Comments can be submitted through the Federal eRulemaking Portal at https://www.regulations.gov. The revisions address the FDA's "current thinking" on selection of patients with early AD for enrollment in clinical trials and selection of endpoints for clinical trials in these populations.

The draft guidance on AD was 1 of 5 documents announced by FDA Commissioner Scott Gottlieb, MD, on February 15, as part of a "new streamlined process for writing science-based, practical guidance documents and getting them out more quickly." The new guidances, Gottlieb said in a press release, "are intended to be concise and free of lengthy narratives that didn't help advance the goals of providing clear scientific feedback" and will not contain information already available in other documents. The other new draft guidances cover drug development in Duchenne muscular dystrophy and closely related conditions, migraine, epilepsy, and amyotrophic lateral sclerosis.

Of the AD guidance, Gottlieb said: "The FDA has been working closely with patients and the scientific community to gain the knowledge that will support intervention in very early AD in ways that have the potential to stop the disease before it causes clinical problems. This document describes innovative approaches to studying very early disease before the onset of dementia, including strategies for trials incorporating patients with Alzheimer's who haven't experienced any visible impairment (in the form of cognitive or functional deficits), but who may be identified through the use of sensitive cognitive screening, imaging tests, or biomarkers."

The announcement encouraging exploration of presymptomatic treatments came at a time of setbacks for several high-profile agents aimed at symptomatic AD. The acceptance of new endpoints (e.g., development versus no development of AD) and new biomarkers is likely to greatly expand the numbers of trials and patients enrolled, as well as produce studies that follow patients for decades rather than months or years.

The complete draft guidance text is available at: https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM596728.pdf.

U.S. Food and Drug Administration

Low-Dose Radiation Research Act of 2017

The U.S. House of Representatives on February 13 passed the Low-Dose Radiation Research Act of 2017 (H.R. 4675). Originally introduced by Representative Roger W. Marshall (R-KS) on December 18, 2017, the bill was referred to the Senate on February 14. The bill would amend the Energy Policy Act of 2005 to provide for a Department of Energy (DOE) basic research program, with an estimated $100 million in federal funds over a 4-y period (FY 2018–2021). The bill identifies 2 main goals: to "enhance scientific understanding of, and reduce uncertainties associated with, the effects of exposure to low-dose radiation" and to "inform improved risk-assessment and risk-management methods with respect to such radiation." The bill calls for rapid DOE development of a 4-year research plan to identify and prioritize basic research needs relating to low-dose radiation.

On January 10, Lamar Smith (R-TX), chair of the U.S. House Committee on Science, Space, and Technology, noted that the bill partially addresses the 2016 closure of DOE's low-dose radiation research program. He stressed the importance of research in exploring unknown health impacts for researchers, industry, health care, and military "as they handle nuclear material, maintain the nation's nuclear weapons program, provide medical treatment, and dispose of nuclear waste." He also cited the importance of information for regulatory agencies that set nuclear safety standards for the public, including federal emergency response agencies, "to more accurately set areas of evacuation for a radiological incident or nuclear power plant meltdown."

Reports in the media and from Representative Marshall have emphasized medical imaging aspects in describing the purpose and intention of the bill. On January 10, when the bill passed through committee review, Marshall, a physician, issued a press release, saying that "Throughout history, radiation has provided vital tools to physicians, from x-rays and CT scans to cutting-edge cancer treatments. Yet we have a limited understanding of the health risks associated with this exposure.. . . For example, an adult patient who receives a CT scan of their torso is exposed to approximately 3 years' worth of background radiation in one scan. While this type of screening is very valuable to countless Americans and often replaces invasive surgical procedures, we physicians are unable to quantify the specific health risks associated with this type of imaging.. . . It is important as radiation screening increases that our doctors have a clear understanding of the health risks associated with this exposure."

The Low-Dose Radiation Research Act of 2017 has received support from the Health Physics Society, the American Association of Physicists in Medicine, the National Council on Radiation Protection and Measurements, and researchers from Northwestern University (Evanston, IL) and Columbia University (New York, NY). The future of the bill in the Senate is uncertain; similar bills have failed in the past.

The U.S. House of Representatives

2017–2026 National Health Expenditures Projections

On February 14 the independent Centers for Medicare & Medicaid Services Office of the Actuary released the projected national health expenditures for 2017–2026. National health expenditure growth is expected to average 5.5% annually over the period, according to a report published ahead of print in *Health Affairs*. Growth in national health spending is projected to be faster than growth in gross domestic product (GDP) by 1.0% during the analysis period. As a result, the report projects the health share of GDP to rise from 17.9% in 2016 to 19.7% in 2026.

The projections indicate that health expenditure rises will be driven primarily by trends in disposable personal income, increases in prices for medical goods and services, and shifts in enrollment from private health insurance to Medicare in an aging population. The report also found that by 2026, federal, state, and local governments are projected to finance 47% of national health spending, up from 45% in 2016. The projections included calculations based on major health provisions from the Tax Cut and Jobs Act and funding throughout the projection period for the Children's Health Insurance Program. The projections do not reflect other health provisions from the Bipartisan Budget Act of 2018.

Additional projections from the report include expectations that Medicare will experience an average annual growth of 7.4%, whereas private health insurance will average 4.7% annual growth. Medicaid is projected to average a 5.8% annual growth, and personal health care spending is anticipated to grow by an annual average of 5.5%. Spending growth is expected to be highest for prescription drugs, growing at an average of 6.3% annually. At the same time, the proportion of the population with health insurance is projected to decrease from 91.1% in 2016 to 89.3% in 2026.

The Office of the Actuary's report is available, with all supporting statistics, at: http://www.cms.gov/Research-Statistics-Data-and-Systems/Statistics-Trends-and-Reports/NationalHealthExpendData/NationalHealthAccountsProjected.html.

Centers for Medicare & Medicaid Services

Mapping the Dopamine System in PD

In an article e-published ahead of print on February 13 in *Movement Disorders*, Fazio et al. from the Karolinska Institutet and Stockholm County Council (Stockholm, Sweden) reported on high-resolution ^{18}F-FE-PE2I PET strategies for detailed mapping of the dopamine transporter (DAT) protein in the nigrostriatal system at the level of cell bodies (in the substantia nigra), axons, and presynaptic terminals (in the striatum). The authors compared DAT protein loss in presynaptic terminals with that in cell bodies and axons in patients with early Parkinson disease (PD). The study included 20 such patients (15 men, 5 women; mean age 62 $\pm$ 8 y) and 20 controls (15 men, 5 women; mean age, 62 $\pm$ 7 y), each of whom underwent ^{18}F-FE-PE2I PET imaging. Binding potential values in the patient group were reduced by 36%–70% in presynaptic terminals and by 30% in cell bodies compared with the control group. DAT availability along the tracts did not differ between the 2 groups. The authors noted that this is the first study to examine DAT protein availability in vivo within the entire nigrostriatal pathway and that the findings "suggest a relative preservation of cell bodies in early PD, which might be relevant for novel disease-modifying strategies."

In a related article on February 13 in News–Medical.Net, senior author Andrea Varrone, MD, PhD, said: "These results suggest that in the early stages of the disease dopamine cells are still viable and that, given the correct treatment, it should be possible to restore their function." He added that "The method we have developed is likely to be able to assist in the diagnosis of Parkinson's disease at an earlier stage and predict the development of the disease. DAT can also be used as a biomarker in clinical trials of new medicines and treatment strategies."

Movement Disorders
News–Medical.Net