Documents for the Record

Subcommittee on Health Hearing
"Check Up: Examining FDA Regulation of Drugs, Biologics, and Devices"
May 22, 2024

Majority:

- May 22, 2024 – Statement submitted by the Alzheimer's Association and Alzheimer's Impact Movement
- May 22, 2024 – Statement submitted by the American Brain Coalition
- May 22, 2024 – Article submitted by Rep. Miller-Meeks
- May 22, 2024 – Document submitted by Rep. Miller-Meeks

Alzheimer's Association and Alzheimer's Impact Movement Statement for the Record

United States House of Representatives Committee on Energy and Commerce, Health Subcommittee Hearing on "Check Up: Examining FDA Regulation of Drugs, Biologics, and Devices"

May 22, 2024

The Alzheimer's Association and Alzheimer's Impact Movement (AIM) appreciate the opportunity to submit this statement for the record for the House Energy and Commerce, Health Subcommittee hearing on "Check Up: Examining FDA Regulation of Drugs, Biologics, and Devices." We are grateful to the Subcommittee and FDA for leading and implementing policies that improve the lives of people living with dementia and their families.

Founded in 1980, the Alzheimer's Association is the world's leading voluntary health organization in Alzheimer's care, support, and research. Our mission is to eliminate Alzheimer's and other dementia through the advancement of research, to provide and enhance care and support for all affected, and to reduce the risk of dementia through the promotion of brain health. AIM is the Association's advocacy affiliate, working in a strategic partnership to make Alzheimer's a national priority. Together, the Alzheimer's Association and AIM advocate for policies to fight Alzheimer's disease, including increased investment in research, improved care and support, and the development of approaches to reduce the risk of developing dementia.

Nearly seven million Americans age 65 and older are living with Alzheimer's dementia in 2024. Total payments for all individuals with Alzheimer's or other dementias are estimated at $360 billion (not including unpaid caregiving) in 2024. Medicare and Medicaid are expected to cover $231 billion or 64 percent of the total health care and long-term care payments for people with Alzheimer's or other dementias, which are projected to increase to nearly $1 trillion by 2050. These mounting costs threaten to bankrupt families, businesses, and our health care system. Unfortunately, our work is only growing more urgent.

Preserving and Strengthening the Accelerated Approval Pathway Program

As you know, accelerated approval is a pathway created by Congress in 1992 and utilized by the FDA to allow for earlier approval of drugs that treat serious conditions and that fill an unmet medical need. Alzheimer's is a deadly disease with no survivors. At each turn when Congress has legislated on accelerated approval, the pathway has been reaffirmed and the Agency has been encouraged to fully harness the promise of the pathway on behalf of patients. Lives have been saved, extended, and improved. Yet there is so much work to be done.

Millions of American families are grateful for these past actions by Congress and fully expect this Congress to continue to support and encourage the use of accelerated approval for all of the patients who today live with unmet medical needs, such as individuals living with

Alzheimer's and other dementia, where treatments are just beginning to emerge, but the unmet need remains vast. The accelerated approval pathway exists so that the FDA can bring urgency and flexibility to the review process, whether that is for a first-of-its-kind treatment or a curative gene therapy. We ask that the FDA and Congress remain committed to preserving the accelerated approval pathway and ensure that all patients living with unmet needs, regardless of their specific conditions, can be assured of the FDA's appropriate utilization of the pathway.

Patients waiting months instead of years for access to treatments has extraordinary meaning to them and their families. Celebrating scientific advancements and innovation and speeding that to patients should not be controversial. In fact, that is how we define success.

Conclusion

The Alzheimer's Association and AIM appreciate the steadfast support of the Subcommittee and its continued commitment to issues important to the millions of families affected by Alzheimer's and other dementia. We would be glad to serve as a resource to the Subcommittee and the FDA as they consider these important issues and how they relate to individuals living with Alzheimer's and related dementias.

Written Statement for the Record
American Brain Coalition
House Committee on Energy and Commerce
Subcommittee on Health
"Check Up: Examining FDA Regulation of Drugs, Biologics, and Devices."
May 22, 2024

On behalf of the American Brain Coalition (ABC), thank you for the opportunity to submit this statement for the record for the Subcommittee on Health's Hearing: *Check Up: Examining FDA Regulation of Drugs, Biologics, and Devices*.

The ABC is a nonprofit organization comprised of over 150 of the nation's leading professional neurological, psychological, and psychiatric associations and patient organizations. Together, the ABC seeks to advance the understanding of the brain and reduce the burden of brain diseases and conditions for millions of Americans.

Brain diseases and conditions encompass a spectrum ranging from neurodegenerative (e.g. Alzheimer's Disease, Parkinson's Disease), neuroimmune (e.g. multiple sclerosis), convulsive (e.g. epilepsy), psychiatric (e.g. schizophrenia, depression), and those caused by insult (e.g. stroke, cerebral hemorrhage and TBI). These conditions not only pose significant challenges to patients and their families but also place a substantial burden on health care systems and society as a whole. Brain disorders and diseases cost the U.S. more than $1.5 trillion per year.

The Food and Drug Administration's (FDA) Neurology Drug Program stands to play a pivotal role in advancing research and innovation in this field, offering hope to those affected by these debilitating conditions. The development of effective treatments and therapies for brain diseases and conditions remains a pressing need. Through targeted investments in research and development, the program has the potential to yield groundbreaking discoveries and transformative therapies that can improve quality of life, alleviate suffering, and ultimately save lives. Continued support for this program will allow the FDA to gain the expertise to develop policies and guidance that keep pace with emerging brain science.

Brain diseases and conditions impose immense hardships on individuals, caregivers, and society at large. The Neurology Drug Program represents a beacon of hope in our collective efforts to combat these debilitating conditions. With targeted investments, this program has the potential to catalyze groundbreaking research, accelerate drug development, and ultimately improve outcomes for individuals living with brain diseases and conditions.

To respond to the unique challenges in the discovery and development of treatments for brain disease, and allow more neuroscience discoveries to directly benefit patients, the federal government must prepare the brain-specific regulatory tools and guidelines needed. These tools should encompass pathways for the creation of novel therapies targeting brain diseases. Additionally, fostering collaboration between regulatory agencies, researchers,

clinicians, and industry stakeholders will be essential to ensure that these tools are grounded in the latest scientific evidence and reflect the diverse needs of patients. By proactively addressing regulatory hurdles and facilitating innovation in the field of neuroscience, FDA can accelerate promising discoveries into safe and effective treatments, improving outcomes for individuals affected by brain disease.

ABC strongly supports the work of FDA in this vein, and we encourage the agency to prioritize the Neurology Drug Program by ensuring it comprehensively addresses the full spectrum of neurologic and psychiatric conditions, advancing innovative treatments. With the support of Congress, FDA can promote improved guidance to aid researchers and product developers in the field of brain and CNS therapeutics, aligning with evolving brain science and promoting prevention, early detection, and treatment. Furthermore, ABC supports FDA's efforts to implement transparent, patient-centric processes for reviewing and approving new treatments and encourages the agency to continue to grow these efforts.

Increased support and funding for the Neurology Drug Program can significantly enhance patient engagement by facilitating the development of more effective treatments and therapies tailored to the diverse needs of individuals with neurological conditions. With greater resources and support, the agency can prioritize patient-centered research initiatives, ensuring that the voices and experiences of patients are central to the drug development process. Ultimately, this could lead to the creation of treatments that are not only more efficacious but also better aligned with patients' preferences, values, and quality of life goals. By investing in and supporting the Neurology Drug Program, we can empower patients to play a more integral role in advancing research and ultimately improving outcomes in the field of neurology. In its role overseeing the FDA, we encourage the Energy and Commerce Committee to prioritize the Neurology Drug Program.

Again, thank you for the opportunity to provide this statement. The ABC looks forward to working together with the committee toward advancements that improve the health of all people living with brain diseases and conditions.

OPINION COMMENTARY Follow

The FDA Wants to Interfere in the Practice of Medicine

A little-noticed provision of the omnibus spending bill could give the agency power to ban off-label use of approved therapies.

By Joel Zinberg

Jan. 12, 2023 6:49 pm ET

Secreted within the 2023 omnibus appropriations bill—4,155 pages, spending $1.7 trillion—is a 19-line section that could change the way medicine is practiced.

Physicians routinely prescribe drugs and employ medical devices that are approved and labeled by the Food and Drug Administration for a particular use. Yet sometimes physicians discern other beneficial uses for these technologies, which they prescribe for their patients without specific official sanction. The new legislation amends the Food, Drug and Cosmetic Act, or FDCA, to give the FDA the authority to ban some of these off-label uses of otherwise approved products. This unwarranted intrusion into the physician-patient relationship threatens to undermine medical innovation and patient care.

The new provision was enacted at the FDA's urging in response to a decision by the U.S. Circuit Court of Appeals for the District of Columbia. The case, *Judge Rotenberg Education Center v. FDA*, involved a 2020 final rule in which the FDA banned the use of an electrical stimulation device, only in the treatment of self-injurious behaviors such as head banging and self-biting. The agency didn't ban other uses of these devices, such as treating addiction.

The court held that the FDA had the power to ban a medical device altogether under Section 360f of the FDCA if it poses "an unreasonable and substantial risk of illness or injury." But barring a practitioner from prescribing or using an otherwise approved device for a specific off-label indication would violate

another FDCA section, which bars the FDA from regulating the "practice of medicine."

The omnibus bill amends Section 360f to allow a finding that a device can pose an unreasonable risk for "one or more intended uses" and ban those uses while leaving it approved for other uses. Since the new provision lets the FDA skirt the ban on interfering with the practice of medicine by banning devices for particular uses, the agency will likely claim this as a precedent allowing it to ban off-label uses of drugs as well.

This is a problem for many reasons. The statute gives the FDA the power, without any public input, to prevent patients' access to off-label therapies even though their physicians and their patients have found the treatments to be beneficial or even essential. That was the situation in the *Rotenberg* case, in which the center and the families of patients had to sue the FDA because the banned devices were often the only effective treatment to keep patients from harming themselves.

Yet 1 in 5 prescriptions written are for an off-label use. In some fields off-label use is the rule, not the exception. In oncology, the standard treatment for specific types or stages of cancer often includes the off-label use of one or more drugs. And off-label uses are routine in pediatrics, where scientific, ethical and logistical concerns preclude conducting large trials for approval in children.

Allowing the FDA to ban certain off-label uses will impair clinical progress. Off-label use enables physicians to assess their patients' unique circumstances and use their own evolving scientific knowledge in deciding to try approved products for new indications. If the treatment proves useful, formal studies are performed and published. If enough evidence accumulates, the treatment becomes the standard of care, even if the manufacturer didn't submit the product for a separate, lengthy and costly FDA review.

Examples abound. Erythromycin, a common antibiotic labeled for use in infectious diseases, is widely used off label to increase stomach motility and tolerance of oral feeding. Clinical use followed by randomized controlled trials established the off-label use of tricyclic antidepressants such as nortriptyline and desipramine as first-line treatments of neuropathic pain. Other antidepressants, such as amitriptyline and trazodone, are prescribed off label as

sleep aids. Rituximab, a lymphoma drug, is used off label to treat a benign disorder, immune thrombocytopenia.

This process works in reverse, too. When evidence accumulates that off-label uses aren't effective, practitioners cease prescribing the drugs for the relevant indications. Ivermectin and hydroxychloroquine, which were advanced and then abandoned as treatments for Covid, are recent examples.

Substituting regulators' wisdom for the cost-benefit judgment of physicians and their patients will discourage attempts to use approved products in new and beneficial ways and deprive patients of valuable treatments. Congress should reconsider this ill-advised legislation.

Dr. Zinberg is a senior fellow at the Competitive Enterprise Institute and director of the Paragon Health Institute's Public Health and American Well-Being Initiative.

The Food and Drug Administration headquarters in White Oak, Md., Aug. 29, 2020. PHOTO: ANDREW KELLY/REUTERS

FDA's Proposed Ban of a Specific Use of a Medical Device (p. 2-3)

When Worlds Collide at the FDA: The Theory of Real-World Evidence Meets Reality

May 14, 2024

By Jeffrey N. Gibbs & Ana Loloei & Véronique Li, Senior Medical Device Regulation Expert —

FDA has long touted the use of **real-world evidence** (RWE). Extolling RWE, FDA has said "RWE can be leveraged to bring new products to market, evaluate the safety and effectiveness of existing products for new uses, and assess the continued performance and safety of products once on the market." FDA recognizes the potential of RWE to support regulatory submissions of medical devices and to inform benefit-risk analysis of such products, while assuring patients have timely access to devices. FDA has even gone so far as to maintain that the "real-life clinical performance of a medical product might be more clearly demonstrated through RWD/RWE because a controlled clinical trial often cannot evaluate all applications of a product in clinical practice across the full range of potential users." However, in our experience, there is a large gap between FDA's lauding the value of RWE and practice.

FDA defines **real-world data** (RWD) as "data relating to patient health status and/or the delivery of health care routinely collected from a variety of sources." RWE is "the clinical evidence regarding the usage, and potential benefits or risks, of a medical product derived from analysis of RWD." RWD can be collected from a wide range of sources, such as electronic health records, registries, administrative claims, pharmacy data, and feedback from wearables and mobile technology.

FDA acknowledges that such data offer opportunities to generate evidence and better understand clinical outcomes. In fact, in 2018, FDA emphasized that leveraging the use of RWD and RWE in regulatory decision-making is "a top strategic priority for the FDA." FDA believes that RWE has the power to "accelerate medical product development and bring new innovations and advances faster and more efficiently to the patients who need them, without compromising patient safety." Further, FDA has stated that enabling advanced data analytics, including RWD, is one of the objectives incorporated in the FDA's Information Technology Strategy for FY 2024-2027.

We, and many stakeholders, agree that RWD and RWE can play an invaluable role. However, based on our experience reviewing device premarket submissions and engaging with FDA, we have found that reviewers have not embraced it in practice. Rather than looking at how RWD/RWE provide meaningful information on safety and effectiveness, reviewers often focus on perceived gaps. But by their very nature, RWD/RWE will have some gaps compared to randomized controlled trials.

Congress has recognized the challenges with FDA's acceptance of RWD and RWE. It was Congress that intervened in 2022, to mandate FDA to issue or revise its 2017 guidance on considerations for the use of RWD and RWE to support regulatory decision-making for devices to clarify its regulatory expectations. Also, under the MDUFA V commitment letter, FDA was directed to continue development of RWD and RWE methods and policies to advance regulatory acceptance for premarket submissions by updating and clarifying the recommendations in the 2017 guidance, and providing RWD/RWE training for FDA review teams, among other things.

In December 2023, FDA issued a new draft guidance on RWE, which updates and clarifies how FDA evaluates RWD to determine if it is sufficient to be used in regulatory decision-making for devices and provides updated recommendations for sponsors collecting RWD. This guidance, when finalized, will replace the original version of this document finalized in 2017.

Of course, as FDA has itself acknowledged, RWE can offer some significant compensatory advantages.

FDA states it has a long history of using RWD and RWE in its regulatory decision-making for devices and conducted a sample analysis of the range of RWE that have been used in regulatory decisions in premarket submissions. Based on a review of premarket submissions made in 2012 through 2019, FDA identified 90 examples of 510(k)s, De Novos, HDEs, and PMAs approved/cleared which utilized RWE in support of regulatory decision-making. During this period the estimated total number of such submissions was approximately 26,121. Based on this data set, RWD/RWE were identified by FDA as being used in a trivial 0.34 percent of examples.

This statistic is consistent with our experience. Similar to FDA's assessment, we have found very few examples where FDA has used RWE as the basis for making a positive regulatory decision in a premarket submission. Not only has FDA not accepted RWD in some cases, it has even raised the evidentiary bar by requiring a clinical study as the only adequate means.

FDA's proposed ban of electrical stimulation devices (ESD) is a case in point. FDA is proposing to ban the device, citing the absence of "large, randomized, and controlled trials, or even any large or randomized trials." (89 FR 20882 at 20889, March 26, 2024). In taking this approach,

FDA expressly rejected the adequacy of the substantial amount of RWD available. Patients that use ESD undergo continuous 24/7 monitoring. There is ample data collected on them during this 24/7 monitoring period such as case notes, contemporaneous patient medical records, and patient tapes. Every use of ESD is recorded, as is every behavior that falls within the intended use. Patients are continually monitored for safety. Far more data are collected at the site than would ever be available in a registry or other source of RWD. Nonetheless, FDA entirely discounted this information and has concluded that the available evidence is not enough to establish ESDs are effective and that instead "randomization, control, [and] large numbers of subjects" should be relied on for understanding the benefit-risk profile of ESDs (89 FR 20882 at 20890). FDA's rejection of all RWD supporting GED in favor of randomized controlled trials cannot be squared with its broader policies. Device stakeholders would be right to be troubled by the inconsistency between FDA's professed support for RWE and its very public rejection of it in the proposed ban.

We recognize that there can be challenges with using RWD/RWE in regulatory decision-making. However, despite FDA leadership's efforts to recognize and encourage use of RWD and RWE, reviewers have not fully embraced RWD/RWE. FDA's brusque rejection of data obtained from 24/7 monitoring of patients, as set forth in its recent proposed ban, will do nothing to encourage reviewers to embrace RWD/RWE.

As FDA has noted, RWD/RWE has the potential to be relied on to evaluate the safety and effectiveness of products. Yet that potential will never be realized unless reviewers are willing to accept RWD/RWE despite their limitations. FDA's recent public dismissal of the use of medical information obtained from continuous, 24/7 monitoring of patients does nothing to encourage reviewers to rely upon RWD/RWE when reviewing marketing submissions.

Categories: Medical Devices