April 4, 2022

The Honorable Patty Murray
Chairwoman
Committee on Health, Education, Labor & Pensions
United States Senate
Washington, D.C. 20510

The Honorable Frank Pallone
Chairman
Committee on Energy and Commerce
United States House of Representatives
Washington, D.C. 20515

The Honorable Richard Burr
Ranking Member
Committee on Health, Education, Labor & Pensions
United States Senate
Washington, D.C. 20510

The Honorable Cathy McMorris Rodgers
Ranking Member
Committee on Energy and Commerce
United States House of Representatives
Washington, D.C. 20515

Dear Chairwoman Murray, Ranking Member Burr, Chairman Pallone, and Ranking Member McMorris Rodgers,

The 91 undersigned organizations, representing patients with rare diseases and other acute or chronic health conditions, urge you to include as part of this year's Prescription Drug User Fee Act (PDUFA) reauthorization provisions to strengthen the Food and Drug Administration's (FDA) accelerated approval (AA) pathway and enable patient access to these critical, often life-saving therapies. The AA pathway has proven itself to be a vital tool in bringing safe and effective treatments to many patients, including those with rare diseases. However, the pathway faces mounting criticism from a variety of stakeholders.[1] Some of these concerns have led to several proposals now before the Department of Health and Human Services (HHS) for consideration, that if approved and implemented, would undermine the authority of the FDA and delay or potentially bar patients from accessing crucial therapies where no other options exist.[2] [3] While there are legitimate criticisms of the AA pathway, too often it appears that issues with accelerated approval are being used as a proxy for the broader health system's challenges with high prescription drug costs. Reducing patient access to therapies that utilize a specific FDA pathway will not solve problems with accelerated approval or prescription drug costs. Therefore, we urge Congress to incorporate into PDUFA reauthorization several recommendations outlined with this letter to strengthen the AA pathway and facilitate patient access to rare disease therapies that utilize accelerated approval.

The History and Importance of Accelerated Approval to the Rare Disease Community

The AA pathway was first enshrined in regulation in 1992, after the HIV/AIDS epidemic had drastically altered the landscape for drug development.[4] In response to the epidemic, scientists sought ways to streamline and expedite clinical trials for HIV/AIDS drugs to focus on the utility of surrogate endpoints which were known to demonstrably correlate with improved outcomes.[5] As consensus grew about the utility of surrogate endpoints in clinical trial design, FDA embraced drug approval reform and promulgated regulations formalizing the AA pathway.[6] Under accelerated approval, the time required to receive FDA approval was considerably shortened allowing for earlier patient access to drugs that were intended to treat serious and life-threatening diseases and conditions for which there were unmet medical needs, including many rare diseases.

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[1] Medicaid and CHIP Payment and Access Commission (MACPAC), *Report to Congress on Medicaid and CHIP*, June 2021, https://www.macpac.gov/wp-content/uploads/2021/06/June-2021-Report-to-Congress-on-Medicaid-and-CHIP.pdf

[2] Oregon Health Authority, *2022-2027 Medicaid 1115 Demonstration Application,* (February 18, 2022), https://www.oregon.gov/oha/HSD/Medicaid-Policy/Documents/2022-2027-Waiver-Application-Final.pdf

[3] Centers for Medicare & Medicaid Services, *Monoclonal Antibodies Directed Against Amyloid for the Treatment of Alzheimer's Disease (CAG-00460N),* (January 11, 2022), https://www.cms.gov/medicare-coverage-database/view/ncacal-decision-memo.aspx?proposed=Y&NCAId=305

[4] The Centers for Disease Control and Prevention ("CDC") published its first report on HIV/AIDS in 1981. See James W. Curran & Harold W. Jaffe, AIDS: The Early Years and CDC's Response, 60 Morbidity & Mortality Weekly Rep. 64 (Oct. 7, 2011), available at https://www.cdc.gov/mmwr/preview/ mmwrhtml/su6004a11.htm.

[5] See U.S. Food & Drug Admin., Guidance for Industry: Human Immunodeficiency Virus-1 Infection: Developing Antiretroviral Drugs for Treatment 3 (Nov. 2015), www.fda.gov/files/drugs/published/Human-Immunodeficiency-Virus-1-Infection--Developing-Antiretroviral-Drugs-for-Treatment.pdf

[6] FDA also created the fast track, breakthrough therapy, and priority review designations to advance the development and review of new drugs and address unmet needs in the treatment of a serious medical condition. See U.S. Food & Drug Admin., Guidance for Industry: Expedited Programs for Serious Conditions – Drugs and Biologics 1 (May 2014) ("Expedited Programs Guidance"), https://www.fda.gov/media/86377/download

It is estimated that 25-30 million Americans (or 1 in 10 individuals) suffer from rare diseases, which are typically serious and life-threatening conditions with unmet medical needs. [7] Of the 7,000 rare diseases that have been identified, more than 90% have no FDA-approved treatment.[8] Many facets of rare diseases make them particularly difficult to study in clinical trials targeting direct clinical benefit. For example, the number of patients with any one condition can be small and heterogeneous, with highly diverse clinical manifestations and a long timeframe for disease progression. Furthermore, there is often a lack of prior clinical studies and a limited number of clinical investigators and treatment centers knowledgeable about a given rare disorder.[9] This makes accelerated approval, and the ability to use surrogate endpoints in the approval process, a particularly important tool for the development of treatments for rare diseases.[10]

Threats to the Accelerated Approval Pathway

Increasingly, the AA pathway, and products that utilize the pathway, are being targeted for differential treatment by various payers in the health care system.[11]

- Institute for Clinical and Economic Review (ICER) and the Medicaid and CHIP Payment and Access Commission (MACPAC) have both advocated for an increase in mandatory federal rebates for accelerated approval drugs until their confirmatory studies are complete and are granted traditional approval.[12] [13]
- Centers for Medicare and Medicaid Services (CMS) has proposed to cover an entire drug class, monoclonal antibodies directed against amyloid for the treatment of Alzheimer's disease, under Coverage with Evidence Development (CED).[14]
- Oregon, as part of their Medicaid 1115 waiver proposal, has requested permission from CMS to exclude Medicaid "coverage of accelerated approval drugs with limited or inadequate evidence of clinical efficacy".[15]

Many critics of the AA pathway claim that these treatments have yet to demonstrate clinical benefit and should therefore be treated differently because they have been studied using surrogate endpoints and are not yet "clinically proven."[16] Furthermore, critics have characterized accelerated approval drugs as "experimental." These criticisms of the AA pathway misunderstand the law and regulations that govern it. Surrogate endpoints are chosen because FDA, in its scientific discretion, has determined they are reasonably likely to predict clinical benefit. Accelerated approval—both as it is set forth in law and in regulations—does not alter FDA's gold

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[7] Jennifer Huron, *New Study Investigates the Number of Available Orphan Products, Generics and Biosimilars*, Nat'l Org. for Rare Disorders (Mar. 25, 2021), https://rarediseases.org/new-study-investigates-the-number-of-available-orphan-products-generics-and-biosimilars/.
[8] *Id.*
[9] Food and Drug Administration. Report: Complex Issues in Developing Drugs and Biological Products for Rare Diseases and Accelerating the Development of Therapies for Pediatric Rare Diseases Including Strategic Plan: Accelerating the Development of Therapies for Pediatric Rare Diseases. July 2014. https://www.fda.gov/media/89051/download
[10] U.S. Food & Drug Admin., CDER Drug and Biologic Accelerated Approvals Based on a Surrogate Endpoint (Jan. 14, 2021), https://www.fda.gov/ media/88907/download
[11] The undersigned organizations may or may not have taken positions on the individual proposals listed below and include them only as context for ongoing discussions on AA.
[12] Institute for Clinical and Economic Review (ICER), *Strengthening the Accelerated Approval Pathway: An Analysis of Potential Policy Reforms and their Impact on Uncertainty, Access, Innovation, and Costs* , (April 26, 2021) https://icer.org/wp-content/uploads/2021/04/Strengthening-the-Accelerated-Approval-Pathway-_-ICER-White-Paper-_-April-2021.pdf
[13] MACPAC, *supra* note 1
[14] Centers for Medicare & Medicaid Services, *supra* note 3
[15] Oregon Health Authority, *supra* note 2
[16] *Id.*

standard of substantial evidence of safety and effectiveness.[17] To the contrary, accelerated approval is granted based on FDA's finding that a drug is safe and effective for its intended use— the same approval standard used for traditional approval. Furthermore, Congress and the FDA have considered – and rejected – the notion that accelerated approval is a different or lesser standard than traditional approval.[18]

Recommendations to Strengthen the Accelerated Approval Pathway

FDA approval is only the first step to a patient obtaining access to a treatment. True access is only achieved when patients receive treatments prescribed and affordably covered by their health program or insurer. Too often this is a serious challenge for rare disease patients. Treating products that utilize accelerated approval differently will not solve these patient access challenges. Therefore, we urge you to focus on advancing legislation to strengthen the pathway and believe the following proposals would do just that while simultaneously alleviating payer concerns and without compromising robust patient access.

Post-market Confirmatory Study Transparency
Post-market confirmatory studies are already a condition of accelerated approval but requiring more robust, frequent, and transparent reports on the design of confirmatory studies and a manufacturers progress on their confirmatory studies would give all stakeholders more confidence that studies are being completed with due diligence. Reports should compare realized progress on the milestones that the manufacturer agreed to at the time of accelerated approval and explain where progress is falling short of the agreement. The FDA should also be required to make this information easily accessible to the public by publishing it on the FDA's website in a timely manner.

Use of Real-World Evidence for Conversion to Traditional Approval
The FDA already utilizes real world evidence (RWE) in the post-market to evaluate safety, and our organizations believe that the FDA should consider, when appropriate, RWE in the post-market in evaluations intended to confirm efficacy in products approved through accelerated approval. Consideration of RWE as part of the evaluation of whether the drug has an effect on the intended clinical benefit would permit FDA to convert accelerated approval drugs to traditional approval, when scientifically appropriate, at an earlier point in time.

Expedited Withdrawal of an Accelerated Approval Product
It can be difficult to design, enroll, and complete post-marketing confirmatory studies for rare disease drugs and there are frequently legitimate reasons for delays in converting a product from accelerated approval to traditional approval. However, delayed confirmatory studies extend prescriber and patient uncertainty and also give fodder to critics of accelerated approval who point to them as evidence that FDA doesn't have the ability to properly address or enforce action against accelerated approval products that have not proven clinical benefit. Establishing clear circumstances under which the expedited withdrawal of an accelerated approval product would be appropriate is important for holding drugmakers accountable for timely completion of confirmatory studies and building confidence in the pathway.

[17] 57 Fed. Reg. at 58944
[18] *See* 158 Cong. Rec. H3825-01, H3848 (2012).

Increased Funding and Resources for FDA
Many of the ideas proposed herein would require additional, targeted resources at FDA. An increase in federal funding and resources through budgeting and appropriations could provide FDA with the resources necessary to implement some of the reforms contemplated and to exercise its existing and ideally expanded authorities when appropriate.

Conclusion

Accelerated approval is critical to the innovation and development of new drugs to treat rare diseases. Our organizations believe these reforms will result in an efficient and transparent use of the AA pathway so that all stakeholders have confidence in products that come onto the market through accelerated approval.

We urge Congress to advance legislation that supports timely patient access to treatments that have been FDA approved through the accelerated approval pathway and strengthens FDA's authority and crucial role in making sure safe and effective drugs are available to improve the health of all people, including those with rare diseases, in the United States. For more information, please contact Heidi Ross, Acting Vice-President of Policy and Regulatory Affairs at the National Organization for Rare Disorders, at HRoss@rarediseases.org.

Thank you for your consideration,

National Organization for Rare Disorders
Alport Syndrome Foundation
ALS Association
American Kidney Fund
Angelman Syndrome Foundation
Angioma Alliance
Arthritis Foundation
Asbestos Disease Awareness Organization
Association for Creatine Deficiencies
Avery's Hope
CACNA1A Foundation
CDG CARE
Child Neurology Foundation
Choroideremia Research Foundation
Conquering Gyrate Atrophy
CSNK2A1 Foundation
Cure CMD
Cure HHT
CureCMT4J
CURED Nfp
Cystic Fibrosis Research Institute (CFRI)
DCM Foundation
Dreamsickle Kids Foundation, Inc
Dup15q Alliance
Epilepsy Foundation
Fabry Support & Information Group
FACES; The National Craniofacial Association
FOD Family Support Group
Foundation for Sarcoidosis Research
Free ME from Lung Cancer
Galactosemia Foundation
Gaucher Community Alliance
Global Healthy Living Foundation
Gorlin Syndrome Alliance
Greater Boston Sickle Cell Disease Association
GRIN2B Foundation
HCU Network America
Hemophilia Federation of America
Hepatitis B Foundation
Hereditary Neuropathy Foundation
Hermansky-Pudlak Syndrome Network
Huntington's Disease Society of America
Huntington's Disease Youth Organization
Hydrocephalus Association
IGA Nephropathy Foundation
Immune Deficiency Foundation
International Foundation for Autoimmune & Autoinflammatory Arthritis (AiArthritis)
International Foundation for CDKL5 Research
International Pemphigus Pemphigoid Foundation

International Waldenstrom's Macroglobulinemia Foundation
JDRF
Lupus Foundation of America
Malan Syndrome Foundation
M-CM Network
MdDS Balance Disorder Foundation
MPN Advocacy & Education International
Muscular Dystrophy Association
National Median Arcuate Ligament Syndrome Foundation Inc
National Multiple Sclerosis Society
National Patient Advocate Foundation
National PKU Alliance
National PKU News
NBIA Disorders Association
NephCure Kidney International
No Stomach For Cancer
NTM Info & Research
Phelan-McDermid Syndrome Foundation
Pulmonary Fibrosis Foundation
Recurrent Respiratory Papillomatosis Foundation
Remember The Girls
RETpositive Inc.
Ring14 USA
SATB2 Gene Foundation
SCID Angels for Life
Sickle Cell Reproductive Health Education Directive
SLC6A1 Connect
STXBP1 Foundation
SYNGAP1 Foundation
The Akari Foundation
The AKU Society of North America
The Association for Frontotemporal Degeneration
The Leukemia & Lymphoma Society
The Life Raft Group
The Patient Story
The RYR-1 Foundation
United Leukodystrophy Foundation
Upstage Lung Cancer
Vasculitis Foundation
VHL Alliance
Williams Syndrome Association
Xia-Gibbs Society, Inc.

CC:
The Honorable Tammy Baldwin, Chair Agriculture Appropriations Subcommittee, U.S. Senate
The Honorable John Hoeven, Ranking Member Agriculture Appropriations Subcommittee, U.S. Senate
The Honorable Sanford Bishop, Chair Agriculture Appropriations Subcommittee, U.S. House of Representatives
The Honorable Andy Harris, Acting Ranking Member Agriculture Appropriations Subcommittee, U.S. House of Representatives