November 2, 2023

The Honorable Bob Casey
Chairman
Senate Special Committee on Aging
G16 Dirksen Senate Office Building
Washington, DC 20510

The Honorable Mike Braun
Ranking Member
Senate Special Committee on Aging
628 Hart Senate Office Building
Washington, DC 20510

Dear Chairman Casey and Ranking Member Braun,

On behalf of the more than 30 million Americans living with one of the over 7,000 known rare diseases, the National Organization for Rare Disorders (NORD) thanks the Special Committee on Aging for the opportunity to provide a statement for the record regarding the Committee's October 26, 2023, hearing titled, "Unlocking Hope: Access to Therapies for People with Rare, Progressive, and Serious Diseases."

NORD is a unique federation of non-profit and health organizations dedicated to improving the health and well-being of people with rare diseases by driving advances in care, research, and policy. NORD was founded 40 years ago, after the passage of the Orphan Drug Act (ODA), to formalize the coalition of patient advocacy groups that were instrumental in passing this landmark law. Since that time, NORD has been advancing rare disease research and funding to support the development of effective treatments and cures; raising awareness and addressing key knowledge gaps; and advocating for policies that support the availability of and access to safe and effective therapies.

Rare disease patients and families need – and deserve – robust evidence to trust in the safety and effectiveness of FDA-approved therapies. Because more than 95% of all known rare diseases do not have an FDA approved treatment,[1] and many rare diseases lead to premature death, often in childhood or adolescence, time is of the essence. NORD encourages Congress to continue to work with the FDA to strengthen rare disease drug development, ultimately bringing more safe and effective therapies to market and addressing the dire unmet medical needs of rare disease patients.[2] Unfortunately, NORD is concerned that S. 1906, the Promising Pathway Act, will ultimately cause more harm than good to the rare disease community, and therefore urge Congress to support more promising, and less perilous, policies instead.

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[1] Fermaglich, L.J., Miller, K.L. *A comprehensive study of the rare diseases and conditions targeted by orphan drug designations and approvals over the forty years of the Orphan Drug Act.* Orphanet J Rare Dis 18, 163 (2023). https://doi.org/10.1186/s13023-023-02790-7

[2] FDA. (2022, March 4). *CDER continues to make rare diseases a priority with drug approvals*. U.S. Food and Drug Administration. Retrieved April 28, 2023, from https://www.fda.gov/news-events/fda-voices/cder-continues-make-rare-diseases-priority-drug-approvals-and-programming-speed-therapeutic

NORD is deeply concerned about the long-term damaging impact the Promising Pathway Act would have on rare disease research and care. The Promising Pathway Act would allow drug companies to market certain drugs as soon as early-stage clinical research is completed, thus bypassing essential steps in the drug development process designed to protect patients from unproven and potentially harmful therapies. Since Congress enacted the Kefauver-Harris Amendments more than 60 years ago in the wake of the thalidomide scandal,[3] carefully controlled clinical investigations of a drug's efficacy have become the hallmark of modern drug development. In fact, the world has followed America's leadership and broadly adopted this gold standard. As tragic examples like the thalidomide scandal demonstrate, carefully controlled clinical investigations are vital to protect patients.[4] Early clinical studies in healthy volunteers and small numbers of individuals with the disease are not sufficient to inform benefit-risk considerations. Every drug has off-target effects that must be carefully balanced against the expected therapeutic benefits, and in many cases, even potentially severe side effects are not detected until the drug is studied in larger and more heterogeneous patient populations during later-stage clinical research. NORD strongly believes the Promising Pathway Act would undermine FDA's long-standing approval standard, exposing patients to unproven and potentially ineffective therapies while exacerbating existing health insurance coverage and reimbursement challenges and undermining international harmonization efforts with other competent regulatory authorities around the world.

Specifically, we urge Congress to not advance the Promising Pathway Act for the following three key reasons:

<u>Early clinical data is a poor predictor of whether a drug will work as intended and leaves patients ill-informed to weigh the benefits and risks of a therapy</u>

Roughly 9 in 10 drugs that are tested in humans are never submitted to FDA for approval.[5] Many drug development programs that look promising in early clinical trials fail during later clinical development. For instance, according to a recent analysis of clinical drug development programs, more than 30% of drugs that enter phase II studies fail to progress to phase III studies, and among those that do progress, more than 58% fail in phase III.[6] Previously unknown toxic side effects were responsible for as many as 50% of failures in phase II trials (the first trials that evaluate a drug in actual patients as compared to healthy volunteers), while insufficient efficacy was responsible for another 30 percent of failures.[7] Safety, as well as efficacy, continue to be

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[3] Greene, J. A., & Podolsky, S. H. (2012, October 18). *Reform, regulation, and pharmaceuticals — the kefauver–harris ...* The New England Journal of Medicine. https://www.nejm.org/doi/full/10.1056/NEJMp1210007

[4] Vargesson N. Thalidomide-induced teratogenesis: history and mechanisms. Birth Defects Res C Embryo Today. 2015 Jun;105(2):140-56. doi: 10.1002/bdrc.21096. Epub 2015 Jun 4. PMID: 26043938; PMCID: PMC4737249.

[5] *22 case studies where phase 2 and phase 3 trials had divergent results*. U.S Food and Drug Administration. (2017, January). https://www.fda.gov/media/102332/download

[6] Van Norman GA. Phase II Trials in Drug Development and Adaptive Trial Design. JACC Basic Transl Sci. 2019 Jun 24;4(3):428-437. doi: 10.1016/j.jacbts.2019.02.005. PMID: 31312766; PMCID: PMC6609997.

[7] Van Norman GA. Phase II Trials in Drug Development and Adaptive Trial Design. JACC Basic Transl Sci. 2019 Jun 24;4(3):428-437. doi: 10.1016/j.jacbts.2019.02.005. PMID: 31312766; PMCID: PMC6609997.

major concerns in phase III studies, with one analysis finding that 44% of the investigated late-phase failures were due to efficacy and 24% due to safety concerns.[8] A set of case studies identified by FDA as illustrative examples for promising phase II programs that ultimately failed in phase III studies identified lack of efficacy in 60% of the case studies, and both safety and efficacy concerns as the key reason for phase III failure in another 30% of case studies.[9] Another analysis of data for more than 185,000 unique clinical trials studying more than 21,000 drug compounds found overall consistent trends; in fact, the probability of success ranged considerably across therapeutic areas, with the lowest probability of success for oncology, followed by areas like central nervous system (CNS) and metabolic or endocrine drugs.[10]

As this data clearly demonstrates, early clinical data provides at best limited and skewed insights into whether – and how well – a drug will ultimately work for patients. By prematurely stopping the clinical development program at this stage, the Promising Pathway Act would risk robbing patients and families of key data and insights necessary to weigh the totality of benefits and risks associated with a treatment. Data from patient registries as outlined in the legislation is not an appropriate substitute for this clinical data. Lowering the bar for FDA approval would ultimately leave many rare disease patients and families without the knowledge that the drugs they take are in fact safe and effective.

Approved yet ineffective drugs can make it much harder for effective drugs to come to market

Once an orphan product has been approved – even if it ultimately turns out that it has limited or no efficacy – it often becomes much harder to bring a second drug to market to treat the same rare disease. This not only includes challenges such as first-to-market advantages, economic challenges associated with raising R&D funding for an orphan disease area with other existing FDA-approved therapies, and challenges with patient identification and recruitment in the often very limited patient populations. In fact, clinical trials often inherently become different, and much harder, to design, conduct, and interpret once a first drug has been approved. Once a drug has been FDA-approved, it usually becomes unethical to conduct a traditional placebo-controlled trial; but, the common non-inferiority trial design that compares the new investigational drug to the approved drug must rely on external data about the already-approved treatment and how well it works.[11] Lack of such robust clinical data about the provisionally approved drug can inadvertently endanger subsequent drug development programs, potentially preventing future, effective treatments from ever coming to market. This can have far-reaching negative consequences for many years to come.

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[8] Van Norman GA. Phase II Trials in Drug Development and Adaptive Trial Design. JACC Basic Transl Sci. 2019 Jun 24;4(3):428-437. doi: 10.1016/j.jacbts.2019.02.005. PMID: 31312766; PMCID: PMC6609997.

[9] *22 case studies where phase 2 and phase 3 trials had divergent results*. U.S. Food and Drug Administration. (2017, January). https://www.fda.gov/media/102332/download

[10] Wong CH, Siah KW, Lo AW. Estimation of clinical trial success rates and related parameters. Biostatistics. 2019 Apr 1;20(2):273-286. doi: 10.1093/biostatistics/kxx069. Erratum in: Biostatistics. 2019 Apr 1;20(2):366. PMID: 29394327; PMCID: PMC6409418.

[11] Center for Drug Evaluation and Research (CDER), & Center for Biologics Evaluation and Research (CBER). (2016, November). *Non-inferiority clinical trials to establish effectiveness guidance for ...* U.S. Food and Drug Administration. https://www.fda.gov/media/78504/download

Provisionally approved drugs may not be accessible to most rare disease patients due to coverage and reimbursement challenges

Rare disease patients already face significant payment and reimbursement challenges in accessing the treatments they need. On average, rare disease patients face direct medical costs of between $8,812 to $140,044 per person per year, compared to $5,562 for those living without a rare disease.[12] Step therapy, other types of utilization management, and coverage and reimbursement challenges related to off-label uses, which are often denied coverage for lack of supporting clinical evidence, force many patients to pay thousands in out-of-pocket cost to access needed therapies – or to completely go without the treatment.[13] This challenge is particularly acute for certain drugs, including several drugs approved through accelerated approval, where CMS and other payors have repeatedly questioned FDA's decision-making and whether the existing evidence is in fact supporting that a drug is appropriate and necessary to treat a given patient. Although the Promising Pathway Act briefly speaks to insurance coverage of provisionally approved drugs, it appears likely that payment and reimbursement challenges for drugs with limited efficacy data will become a major obstacle for our patients, whether in form of outright coverage and reimbursement denials, through excessive step therapy and other utilization management tools, or through other approaches such as exclusion from formularies. In addition, this legislation may further undermine coverage and reimbursement for orphan drugs more broadly by increasing confusion and undermining trust in FDA's long-standing gold standard for approval. The best therapy is useless to those patients who cannot afford to access it, and without timely insurance coverage, large parts of our patient populations may be shut out from accessing drugs that obtained provisional approval.

Rather than supporting legislation that will ultimately be detrimental to the rare disease community, NORD urges Congress to further policy initiatives that would strengthen orphan drug development and give more rare disease patients timely access to life-changing therapies.

Strengthen policies that allow more patients to enroll and remain in clinical trials, improve the probability of successful rare disease drug development programs, and speed up the path to market

Clinical trials are often the best – and only – hope for rare disease patients. Yet, rare disease patients face many barriers to trial participation. At the same time too many rare disease trials fail due to recruitment and retention issues. Ensuring the maximum number of rare disease patients can benefit from clinical trials will help address the unmet medical need of the rare disease community while supporting broader rare disease drug development. Carefully calibrating and enhancing trial eligibility criteria, enrollment practices, and trial designs to ensure

[12] NCATS Alliance. (2021, October 22). *NIH study suggests people with rare diseases face significantly higher health care costs*. National Institutes of Health. https://www.nih.gov/news-events/news-releases/nih-study-suggests-people-rare-diseases-face-significantly-higher-health-care-costs

[13] Fung A, Yue X, Wigle PR, Guo JJ. Off-label medication use in rare pediatric diseases in the United States. Intractable Rare Dis Res. 2021 Nov;10(4):238-245. doi: 10.5582/irdr.2021.01104. PMID: 34877235; PMCID: PMC8630459.

trials work for rare disease patients is a critical first step to ensuring equitable access.[14] Decentralizing clinical trials and leveraging digital health technologies (DHTs) to bring trials into the community and closer to our patients are another important part of the equation. NORD appreciates FDA's past and current efforts to make clinical trials work better for rare disease patients and families and urges Congress to continue to work with FDA and all stakeholders to break down barriers to fair and equitable trial participation.[15,16]

Ensuring promising rare disease drugs have a timely, clear and consistent path to market is another key component in supporting rare disease drug development. Various FDA pilot programs and initiatives are designed to do exactly this, including the "Support for Clinical Trials Advancing Rare Disease Therapeutics" (START) Pilot Program, which supports enhanced early interactions between drug sponsors and FDA reviewers,[17] and the "Rare Disease Endpoint Advancement Pilot Program" (RDEA Pilot) which aims to "provide mechanisms to sponsors to collaborate with FDA throughout the efficacy endpoint development process."[18] Similarly, efforts to strengthen and expand the use of real-world data (RWD) and real-world evidence (RWE), as well as novel and innovative data sources including digital twins and other artificial intelligence based data can help speed time to market and reduce or eliminate the number of patients on placebo arms. We urge Congress to ensure FDA can appropriately fund and scale these programs, and to ensure the timely evaluation and assessment of these initiatives to determine which ones work and should be expanded – and which ones fall short of expectations and need to be revised or reimagined.

Strengthen and improve FDA's expanded access program

Even if access to robust clinical trials for rare disease patients is significantly improved and streamlined, it will not be feasible for all patients who may benefit from an investigational treatment to participate in clinical trials. In these situations, the FDA's expanded access program provides certain patients with serious or life-threatening diseases who cannot participate in a clinical trial an alternate pathway to access an investigational drug. FDA consistently receives more than 1,800 applications for expanded access per year, and on average approves over 95%

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[14] Center for Drug Evaluation and Research (CDER), & Center for Biologics Evaluation and Research (CBER). (2020, November). *Enhancing the diversity of clinical trial populations — eligibility ...* U.S. Food and Drug Administration. https://www.fda.gov/media/127712/download

[15] Center for Drug Evaluation and Research, Center for Biologics Evaluation and Research, Center for Devices and Radiological Health, & Oncology Center of Excellence. (2023, May). Decentralized Clinical Trials for Drugs, Biological Products, and Devices. U.S. Food and Drug Administration. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/decentralized-clinical-trials-drugs-biological-products-and-devices

[16] Center for Drug Evaluation and Research. (2023). *CDER Conversation with Leonard Sacks.* U.S. Food and Drug Administration. https://www.fda.gov/drugs/news-events-human-drugs/evolving-role-decentralized-clinical-trials-and-digital-health-technologies

[17] Office of the Commissioner. (2023). *FDA launches pilot program to help further accelerate development of rare disease therapies*. U.S. Food and Drug Administration. https://www.fda.gov/news-events/press-announcements/fda-launches-pilot-program-help-further-accelerate-development-rare-disease-therapies

[18] Center for Drug Evaluation and Research. (2022). *Rare disease endpoint advancement pilot program*. U.S. Food and Drug Administration. https://www.fda.gov/drugs/development-resources/rare-disease-endpoint-advancement-pilot-program

of these applications.[19] Emergency requests for single-patient treatment are consistently reviewed within less than a day, and CDER on average reviews non-emergency single-patient requests within less than 8 days.[20] Yet, although survey results indicate that as many as 94% of physicians would recommend expanded access to their colleagues, challenges accessing the program due to administrative burdens, lack of awareness, and little to no financial incentives for sponsors to provide expanded access continue to hamper the program.[21] We urge Congress to work with FDA to further strengthen the expanded access program so that individual patients who have limited or no other options for accessing investigational therapies have access to a clear, transparent, and predictable process while maintaining the integrity of ongoing clinical research programs.

Just as NORD fought for the enactment of the Orphan Drug Act four decades ago, NORD will continue to advocate for policies that further rare disease drug development and enable patient access to new and better treatments. In keeping with NORD's mission to promote the best interests of the rare disease community, we continue to oppose the Promising Pathway Act and instead advocate for constructive, tangible policy proposals that will meaningfully improve rare disease drug development.

Again, NORD thanks the Special Committee on Aging for the opportunity to provide a statement for the record on the Promising Pathway Act and we look forward to continuing the dialogue around strategies to bring safe and effective rare disease drugs quickly and effectively to patients. For questions regarding NORD or the above comments, please contact Karin Hoelzer, DVM, PhD, Director, Policy and Regulatory Affairs at khoelzer@rarediseases.org or Heidi Ross, MPH, Vice President, Policy and Regulatory Affairs at HRoss@rarediseases.org.

Sincerely,

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Director, Policy and Regulatory Affairs
National Organization for Rare Disorders

Heidi Ross, MPH
Vice President, Policy and Regulatory Affairs
National Organization for Rare Disorders

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[19] *Expanded Access Program Report - U.S. Food and Drug Administration*. Food and Drug Administration. (2018). https://www.fda.gov/media/119971/download?attachment

[20] Ibid.

[21] Bunnik EM, Aarts N, van de Vathorst S. The changing landscape of expanded access to investigational drugs for patients with unmet medical needs: ethical implications. J Pharm Policy Pract. 2017 Feb 21;10:10. doi: 10.1186/s40545-017-0100-3. PMID: 28239479; PMCID: PMC5320715.