December 4, 2023

Re: The Promising Pathway Act, S. 1906/H.R. 4408

Dear Senators and Representatives,

We are a group of clinicians, lawyers, advocates, and others with expertise in FDA drug regulation, clinical research and practice, and bioethics writing to express concern regarding the proposed Promising Pathway Act (S. 1906/H.R. 4408). Importantly, this concern is shared by the National Organization for Rare Disorders (NORD) and the Pharmaceutical Research and Manufacturers of America (PhRMA), demonstrating that you can support patients and the pharmaceutical industry without supporting this bill.

Like you, we share the goal of helping patients with rare, serious diseases live better and survive longer. However, weakening FDA approval standards, as this bill proposes, risks conflating the essential goal of getting patients access to more drugs that work with the misguided goal of simply getting them more drugs. In this letter, we explain the following key points and note how Congress can play a meaningful role in facilitating development of novel products for devastating diseases.

- **The Promising Pathway Act is unnecessary.** FDA’s regulatory standards for drugs to treat rare and serious diseases are already flexible, sometimes allowing approval based on weak evidence. In addition, FDA and other agencies have recently launched several efforts to encourage discovery, development, and timely access to effective treatments.

- **The Promising Pathway Act will harm patients.** Eroding regulatory standards will leave patients and their doctors with inadequate evidence to inform treatment decisions. It will also entrench inadequate treatments by making it difficult to study potentially better options. The post-approval registries required by the proposed Act cannot resolve these concerns.

- **The Promising Pathway Act addresses the wrong end of the problem.** The real bottlenecks to treating many rare and serious diseases are scientific challenges that lie far upstream from FDA approval. To ensure that patients have more drugs that will meaningfully improve their lives, we urge Congress to reject the PPA and (1) ensure robust funding for rare disease research, (2) improve access to clinical trials, (3) promote broader use of FDA’s Expanded Access pathway, (4) clarify FDA’s authority to require and enforce rigorous trials to confirm drugs’ benefit and safety after approval, and (5) adequately fund FDA.
If passed, the Promising Pathway Act (PPA) would amend the Federal Food, Drug, and Cosmetic Act to establish a new “provisional” approval pathway for drugs intended to treat, prevent, or diagnose a serious or life-threatening disease or condition. Provisional approval would be effective for a 2-year period and renewable for up to 8 years total. Importantly, the pathway would not be restricted to drugs intended to treat rare diseases or diseases with limited or no available treatments, despite the framing of the Senate Aging Committee’s October 26, 2023, hearing on the PPA.

The PPA’s proposed standard for provisional approval would be much weaker than FDA’s current statutory standard, which requires “substantial evidence” of effectiveness. Typically, this means that at least one well-designed clinical trial demonstrates the drug works and is sufficiently safe. By contrast, the PPA would allow provisional approval based on “relevant early evidence” of a “positive therapeutic outcome.” The bill fails to define these phrases, while referencing “early-stage clinical investigations.” This language clearly contemplates approval based on Phase 2 trials, which primarily measure safety in the intended patient population and offer only preliminary assessments of efficacy. However, it could also support approval based on Phase 1 trials that first test a drug in people or statistically problematic post-hoc (unplanned) analyses. These approaches will leave patients in the dark about whether a drug works and for whom, as well as how to use effective drugs to maximize benefit and minimize risk.

Unfortunately, drugs that look promising in early development or based on unplanned analyses of subsets of trial participants often fail to have their benefit confirmed in later studies.\(^1\textsuperscript{-3}\) For example, it is possible that the PPA’s weak standard might have sufficed to provisionally approve NurOwn, an investigational stem cell therapy for amyotrophic lateral sclerosis (ALS) that failed to demonstrate benefit on any measure outside unplanned subgroup analyses and anecdotal examples.\(^4\textsuperscript{-5}\) Although some advocating for the PPA view NurOwn as an example of why the bill is needed, what it truly demonstrates is that the bill might serve as an 8 year-long free pass for companies to profit from drugs they fail to demonstrate work. In fact, despite the purported expiration date for provisional approval, it is likely that FDA will face pressure to grant traditional approval at the end of 8 years rather than withdrawing drugs from the market, regardless of remaining evidentiary gaps. This problem is evident in FDA’s existing accelerated approval pathway, under which drugs have been allowed to remain on the market for extended periods despite substantial delays in completing required studies and failure to demonstrate meaningful benefit.\(^6\textsuperscript{-8}\) Desperate patients deserve better.

Although no patient would be forced to accept a provisionally approved drug, that does not mean the PPA would not affect them – weakened FDA approval standards harm all patients. This is because one of FDA’s most important roles is to ensure that companies produce information that patients and clinicians need to guide treatment decisions.\(^9\) Companies cannot sell their drugs – and therefore cannot profit – until they generate enough evidence to convince FDA the drug is sufficiently safe and effective. As a result, companies seek to generate the evidence FDA demands. If the PPA authorizes FDA to demand less, however, patients and clinicians will have less. One must look only as far as the dietary supplement industry to see how this plays out: imagine if what you had available to treat your life-threatening illness was rows of products none of which you knew worked at all, let alone which was most appropriate for you or how it should be taken to maximize effect. This is the future envisioned by the PPA.

Importantly, weak approval standards can entrench poor treatments by making it difficult to study potentially better options.\(^10\) When an unproven drug becomes available through FDA approval, it can reduce patient willingness to enroll in subsequent trials, especially because approval often signals that a drug is worth trying. To enroll patients, then, it may be necessary to
compare new drugs to approved but unproven products, making it much harder to interpret trial results. This leaves future patients no better off than those facing terrible diseases today.\textsuperscript{11-13} FDA should not be expected to approve new drugs – provisionally or otherwise – simply because desperate patients would be willing to try them;\textsuperscript{5} that is not what patient-focused drug development calls for. Such a standard for approval would dangerously ignore FDA’s critical public health mission and risk inhibiting development of effective drugs.\textsuperscript{14,15}

The PPA’s solution for weak provisional approval is to require that treated patients participate in “an observational registry” until either the drug is granted traditional approval or provisional approval is rescinded. Under such a registry, information will be collected about patients taking the drug. However, registries do not involve randomization or blinding, and they lack concurrent control groups of patients not taking the drug to provide data for comparison, all of which are critical design features that help make clear whether any benefits experienced by patients are due to the drug and not something else.\textsuperscript{16-18} These design features are especially important when a disease is heterogenous in how it affects patients, its natural history is not well understood, or a drug’s effect size is modest, all of which are often true. Yet the PPA does not require any additional studies beyond the registry, and instead, directs FDA to allow use of real-world evidence (such as a registry study) to fulfill follow-up requirements and support applications for traditional approval. It also directs FDA to “consider the option to waive requirements for adequate and well-controlled studies” when determining whether a provisionally approved drug should move to traditional approval. Accordingly, the bill appears to contemplate registry data serving as the exclusive mechanism to confirm drug benefit, even though registries are usually incapable of demonstrating a drug’s effectiveness, even for rare diseases. This is one of the PPA’s most worrisome shortcomings.

Overall, the PPA would set the bar too low for both provisional approval and later demonstration of benefit. We recognize, however, that it is reasonable for FDA to tolerate greater uncertainty when considering drugs for serious diseases without adequate treatment options. Importantly, the agency already uses its expansive regulatory flexibility to do just that. FDA is granting accelerated approvals more frequently and more broadly than in the past, moving beyond oncology to neurodegenerative diseases, among others.\textsuperscript{6,19} Even for diseases that lack plausible surrogate markers to support accelerated approval, the agency has demonstrated willingness to approve drugs even when trials fail to show benefit on pre-specified endpoints including those meaningful to patients, when benefit is supported by just one pivotal study, and when trials are very small or lack control groups.\textsuperscript{20-25} Although there is often discussion about how long it takes to run trials, over half of approved orphan drugs were supported by trials lasting less than one year and about one-third were approved based on trials lasting 6 months or less.\textsuperscript{25} In addition, FDA’s review times are faster than those of both the European Medicines Agency (EMA)\textsuperscript{26} and Health Canada,\textsuperscript{27} and FDA approves most novel drugs before they are approved anywhere else in the world.\textsuperscript{28,29}

The fact is that FDA is simply not refusing to approve good drugs. To the contrary, rather than requiring too much evidence to support approval, in some cases it is appropriate to question whether FDA is requiring too little. Unfortunately, the agency’s current flexibility is not always met with rigorous or timely confirmation of benefit after approval.\textsuperscript{6,12,30} The response should not be to further weaken drug approval standards, as the PPA proposes, but rather to ensure that approvals are at least based on strong expectations of benefit and followed by rapid, high-quality evidence generation post-approval.\textsuperscript{31}

Ultimately, the reason many serious and life-threatening diseases currently lack good treatment options is not because FDA is standing in the way but because there are gaps in scientific
understanding upstream from the regulatory approval process. Therefore, **the strongest path forward is to address scientific bottlenecks.** FDA and others have already taken important steps in this direction and need adequate funding to continue this trajectory. For example, FDA recently launched “Support for Clinical Trials Advancing Rare disease Therapeutics” (START), a pilot program informally dubbed “Operation Warp Speed for rare diseases,” which will provide real-time advice to companies starting early in drug development to speed successful trials and address manufacturing issues. The agency has also established the **Rare Disease Endpoint Advancement (RDEA) pilot program** to support novel efficacy endpoint development for drugs to treat rare diseases. In addition, **FDA's Action Plan for Rare Neurodegenerative Diseases** and its ALS **Science Strategy** emphasize improved scientific understanding of rare disease through characterizing disease development and natural history, facilitating access to clinical trial participation through decentralized models, enhancing trial infrastructure, adopting innovative trial designs to support the development of better drugs and novel statistical approaches for small populations, and incorporating “Expanded Access” into clinical development programs (an approach that allows seriously ill patients to access unapproved drugs outside trials under certain conditions). Importantly, **these efforts focus attention on improving science rather than weakening approval standards.**

While the science continues to develop for rare diseases lacking good treatment options, Congress can most productively improve access to effective medicines by:

1. **Ensuring robust funding for rare disease research,** including efforts to improve prevention, speed of diagnosis, and biomarker development, as well as grant programs to support development of promising drugs by small companies with limited capital;
2. **Promoting clinical trial accessibility,** including through decentralized approaches;
3. **Encouraging broader use of FDA's Expanded Access pathway** prior to drug approval and overcoming existing hurdles related to physician and community awareness, company disinterest, and cost;
4. **Clarifying that FDA has authority to require and enforce rigorous post-market efficacy studies** whenever it approves a drug with uncertain benefit; and
5. **Providing FDA with sufficient funding** to support the agency’s current efforts to offer nuanced regulatory guidance for rare disease drug development.

**We urge you to reject the Promising Pathway Act, which lacks the support of both NORD and PhRMA.** Like us, PhRMA warns that the PPA “poses serious concerns that run counter to the goal of helping patients access safe and effective medicines,” while NORD emphasizes that “[a]pproved yet ineffective drugs can make it much harder for effective drugs to come to market” and notes that the PPA will “ultimately cause more harm than good to the rare disease community.” Unfortunately, the bill is beyond repair because its central premise would undermine FDA’s standards for drug approval, ensuring earlier profit for companies but not better drugs for patients. Instead, we urge you to take the alternative steps outlined above to truly stimulate and support the development of novel and needed drugs. We welcome the opportunity to engage further. Thank you for your commitment to these important issues.

Sincerely,

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cc: House co-sponsors: Representatives Westerman, Fitzpatrick, D’Esposito, Quigley, Swalwell, and Phillips

cc: Additional members of the Senate HELP Committee: Senators Murray, Baldwin, Kaine, Smith, Hickenlooper, Murphy, Hassan, Luján, Markey, Paul, Marshall, Tuberville, Budd, Collins, Romney, and Mullin

cc: Additional members of the Senate Special Committee on Aging: Senators Blumenthal, Warren, Kelly, Fettermen, Scott, Rubio, and Scott


cc: Additional members of the House Health Subcommittee: Representatives Bucshon, Burgess, Latta, Griffith, Bilirakis, Johnson, Hudson, Carter, Dunn, Pence, Crenshaw, Joyce, Harshbarger, Miller-Meeks, Obernolte, Sarbanes, Cardenas, Ruiz, Dingell, Kuster, Kelly, Barragán, Rochester, Craig, Schrier, and Trahan

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