Subcommittee on Aging
Hearing on "Unlocking Hope: Access to Therapies for People with Rare, Progressive, and Serious Diseases"

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SUMMARY

- FDA already has and exercises substantial regulatory flexibility to approve promising drugs for rare, serious diseases. Where it needs additional adjustment is in requiring rigorous follow-up studies after approval to confirm these drugs are truly beneficial.
- The Promising Pathway Act would set the bar for provisional approval and later confirmation of drug benefit too low, resulting in more drugs on the market, but not necessarily more drugs *that work* to treat people with rare, serious diseases.
- Weak approval standards inhibit development of evidence that all patients need to guide treatment decisions and risk interfering with development of other possibly better drugs.
- Patient registries have limited ability to demonstrate drug effectiveness because they lack randomization and blinding; observed differences in outcomes may therefore result not from the drug, but from other differences between patients. This is especially true when the disease is heterogenous, its natural history is not well understood, or a drug's effect is small.
- The Promising Pathway Act faces additional shortcomings as currently drafted, including lack of clarity about how a drug moves from provisional to traditional approval and requirements for provisional approval to be renewed.
- FDA and NIH have undertaken a variety of efforts, including recent initiatives, to support scientific advancement in rare disease drug development and to reduce regulatory burden.
- This committee can help facilitate the goal of improving access to effective rare disease treatments by: (1) ensuring funding for rare disease research and efforts to promote clinical trial accessibility; (2) encouraging use of FDA's expanded access pathway; and (3) clarifying that FDA has the authority to require and enforce post-market efficacy studies whenever it approves a drug with uncertain benefit, in order to ensure patients, clinicians, and payers all have the confirmatory evidence they need.

Senator Casey, Ranking Member Braun, and distinguished Members of the Committee, thank you for convening this important hearing and inviting me to testify. I am grateful for the opportunity to submit written comments in addition to my hearing testimony to inform a goal we all share: helping patients with rare, serious diseases live better and survive longer.

BIOGRAPHY

My name is Holly Fernandez Lynch. I am a bioethicist and attorney by training. I'm also an assistant professor of medical ethics and law at the University of Pennsylvania, which has asked me to note that opinions expressed in this testimony do not necessarily represent those of the University of Pennsylvania Health System or the Perelman School of Medicine. My remarks also should not be attributed to the National Academies committee on which I currently serve, focused on accelerating treatments and improving quality of life for people living with amyotrophic lateral sclerosis (ALS), or to any other organization with which I am affiliated. I receive research funding from Arnold Ventures to study issues relevant to this hearing, but no funder has played a role in preparing this testimony.

I obtained my JD and master's degree in bioethics from the University of Pennsylvania in 2006. I worked as an associate attorney in the pharmaceutical and biotechnology practice group at Hogan Lovells (then Hogan & Hartson), where I was trained in FDA law and policy and gained exposure to the world of clinical research and regulation and FDA approval standards. I then served as a bioethicist in the Human Subjects Protection Branch at the National Institutes of Health (NIH) Division of AIDS. There, I helped address ethical challenges arising in US and global HIV prevention and treatment research. I next served as a senior policy and research analyst supporting President Obama's Commission for the Study of Bioethical Issues, where I worked on reports addressing historical research ethics abuses and improving modern research protections. Immediately before returning to Penn, I served as the executive director of the Petrie-Flom Center, a health policy and bioethics research program at Harvard Law School, teaching and mentoring students and leading research to improve clinical trial participation, conduct, and oversight, among a variety of other projects.

I joined the faculty at Penn in 2017, with a primary appointment in the medical school and secondary appointment in the law school; I have recently been promoted to associate professor, effective July 2024. I also serve in several national leadership roles, including President-elect of the board of directors for the American Society of Law, Medicine, and Ethics and board director for Public Responsibility in Medicine & Research. I founded and co-chair the Consortium to Advance Effective Research Ethics Oversight, an organization that aims to define, measure, and improve the quality of Institutional Review Boards (IRBs) responsible for protecting the rights and welfare of research participants. In addition, I served as a member of the US Department of Health and Human Services Secretary's Advisory Committee on Human Research Protections (SACHRP), offering expert advice and recommendations on government research regulations and policy. Finally, I am an active member of the Compassionate Use and Preapproval Access Working Group at the NYU's Grossman School of Medicine.

Informed by this experience, my scholarship focuses on FDA drug approval policy, access to investigational medicines before FDA approval, and clinical research ethics, regulation, and oversight. **The overarching question that drives my research is this: how should we balance speed and certainty in decisions that affect access to new drugs?** This question raises important ethical issues regarding respect for autonomy, informed decision-making, avoidance of exploitation, and promotion of benefit for individual patients and broader populations, both in the present and the future. The question is also informed and affected by legal levers that influence what sort of evidence is generated and when. I have published extensively in this space and would be happy to provide copies of relevant articles.[1–14]

Although I have bioethics and legal expertise that I hope this committee will find useful, I have no immediate personal stake in the outcome of this hearing, as I am not myself facing a rare, serious disease. I recognize that some believe lived experience is the only credential relevant to these policy issues and I certainly agree that personal experience is valuable in this context.[15] However, the sad reality is that rare, serious diseases are not rare in the aggregate. Any one of us could find ourselves and our loved ones affected at any time. We all have an interest in these important issues and I care about them deeply, for the sake of all who are suffering today and all who may be suffering tomorrow.

MY KEY MESSAGE TO THE COMMITTEE

With the help and guidance of some tremendous advocates, my work has led me to better understand the deep challenges facing the community of people living with and affected by ALS, as well as other rare and life-threatening diseases that lack good treatment options. From the "Right to Try"[16] to the "Promising Pathway Act," I have seen patients and advocates seek legislative solutions that they hope will provide speedier access to new drugs, emphasizing their willingness to accept great uncertainty and risk in pursuit of something – anything – that will work. I understand these approaches and why they seem attractive. However, I accepted the Committee's invitation to testify because I believe we must be wary of unintended consequences in efforts to promote access to unproven drugs.

My key message is that we must avoid approaches that displace the essential goal of getting patients more drugs *that work* with the deflated goal of simply getting them more drugs. That is the risk posed by the Promising Pathway Act.

FDA'S EXISTING REGULATORY FLEXIBILITY

To be clear, **I support regulatory flexibility in FDA drug approvals.** By statute, FDA must determine that new drugs are safe and effective – a standard that requires both scientific assessment and policy judgment.[17] The real question is whether a drug is safe and effective *enough*, given the disease at hand. Context matters and it is reasonable to accept less certainty about a drug to treat ALS or a fatal pediatric disorder than a drug to treat migraines.

With that in mind, it is essential to acknowledge that **FDA already has tremendous regulatory flexibility for serious diseases with unmet treatment needs – and the agency often uses it.** Importantly, however, regulatory flexibility does not mean that every drug is or should be approved.

Perhaps the most well-known type of flexibility available to FDA is accelerated approval, which allows certain drugs to be approved based on measures other than those directly

assessing how a patient feels, functions, or survives. Accelerated approvals are granted based on a reasonable prediction of benefit supported by a drug's impact on unproven surrogate or intermediate endpoints, such as reduction in certain biomarkers in the blood or brain. They are followed by required post-market trials to confirm whether the predicted benefit is real; if benefit is not confirmed, FDA may utilize an expedited process to withdraw approval. Accelerated approvals are on the rise, including outside oncology and in the neurodegenerative disease space.[18,19] However, more than a third of accelerated approvals have incomplete confirmatory trials, and a third of those are past their due dates, with uncertainty dragging on for patients – including for very pricey drugs.[18] In addition to delays, the quality of confirmatory trials is often questionable and it can be difficult to withdraw approvals even when confirmatory trial results fail to show benefit.[5,20] These problems challenge the accelerated approval compromise, which is intended to provide speedy access to promising drugs now with evidence of benefit later.

Beyond accelerated approval, FDA also has other types of flexibility. Most importantly, **the agency can and does approve drugs even when trials fail to show benefit on pre-specified endpoints**. For example, FDA approved Biogen's Qalsody (tofersen), a drug to treat a rare genetic type of ALS, even though the trial did not meet its primary or secondary endpoints. The agency has also approved drugs for other rare diseases despite failed trials, including an ultra-rare connective tissue disorder called fibrodysplasia ossificans progressive (FOP) and Duchenne's muscular dystrophy.[21] In fact, 10% of the drugs FDA approved between 2018-2021 had pivotal trials with null findings.[22] I also want to be clear that FDA does not require a demonstrated survival benefit for drug approval, nor does it require that benefit be demonstrated in all study participants, although these are misconceptions I often hear; demonstrated or likely functional benefit in a subgroup of the trial population can also suffice, especially if the trial was well-designed to measure that outcome.

Finally, **FDA has demonstrated an increased willingness to approve drugs based on just one pivotal trial rather than the gold standard of at least two adequate and well-controlled clinical investigations**. In 2022, 65% of drug approvals were supported by a single efficacy study,[23] including Amylyx's ALS drug, Relyvrio (sodium phenylbutyrate and taurursodiol), which the European Medicines Agency (EMA) has refused to approve until it can

review results of an ongoing Phase 3 trial given uncertainty about the drug's benefit. Moreover, FDA is not demanding perfection from the single studies supporting these approvals; they are often not randomized, without concurrent controls, and lack results with exceptionally strong statistical significance.[24]

Importantly, **when FDA grants early approval to drugs with uncertain benefit outside the accelerated approval pathway, it does not require companies to complete additional studies to ensure that benefit is confirmed**.[2] It is that disconnect between early approval and confirmation of efficacy that especially concerns me.[2] Unfortunately, I fear **the Promising Pathway Act would inadvertently exacerbate the problem**.

PRIMARY CONCERNS REGARDING THE PROMISING PATHWAY ACT

The proposed Promising Pathway Act would create a new category of "provisional approval" for drugs intended to treat, prevent, or diagnose a serious or life-threatening disease or condition, followed by required patient registries that FDA would be required to review annually to assess the drug's "side effect profile" in relation to its benefit.

Especially because I know many have worked hard on this piece of legislation, let me start with the bill's strengths. First, it would impose automatic expiration dates on provisionally approved drugs, with 2-year terms that may be renewed for a total maximum period of 8 years. That's helpful because **it is a step in the right direction to limit how long drugs with uncertain benefit are allowed to remain on the market**. Second, the bill would require that further data be collected from all patients receiving a provisionally approved drug. Although the approach the bill takes to that data collection has shortcomings as described below, it is at least an important acknowledgment that **uncertain approvals should always be followed with additional evidence**. Third, the bill would require specific informed consent from patients prescribed a provisionally approved drug, acknowledging that it did not undergo the usual process for FDA approval, and explicit acknowledgment of provisional approval status in all drug labeling and promotional materials. Both steps would help **draw patient and clinician attention to relevant shortcomings in the evidence supporting the drug**, an improvement

over current approaches that may lead to confusion over the evidence supporting accelerated approval drugs or those approved through other types of regulatory flexibility.[25]

Despite these strengths, the bill raises important concerns, including several that leading experts in FDA pharmaceutical law, policy, and ethics shared with Senator Braun's office in 2020 in the context of this bill's predecessor, the Conditional Approval Act.[26] **In sum, the Promising Pathway Act would set the bar for both provisional approval and later confirmation of drug benefit far too low.**

THE PROBLEM WITH WEAK APPROVAL STANDARDS

Rather than the current evidentiary standard for drug approval, which requires "substantial evidence" of effectiveness, **the Promising Pathway Act would allow approval based on "relevant early evidence" from "adequate and well-controlled investigations, including early-stage clinical investigations" to establish that the drug provides "a positive therapeutic outcome," a much lower standard**. The phrases "relevant early evidence" and "positive therapeutic outcome" are not further defined and it is unclear what the lower evidentiary bound might be. Could relevant early evidence come from Phase 1 trials or unplanned post-hoc analyses? What drugs couldn't be approved on this standard?

Unfortunately, many drugs look promising in early development or based on various unplanned subgroup analyses, only to fail to demonstrate benefit in later studies. To take one example, in dexpramipexole's Phase 2 trial, ALS patients receiving the highest dose saw almost 50% slower decline in muscle function than those receiving placebo, although other results were marginal. In the Phase 3 trial conducted in nearly 1000 ALS patients across 11 countries, however, the drug was not effective in slowing loss of muscle function or improving survival.[27]

In another salient example, BrainStorm's investigational stem cell therapy for ALS, debamestrocel (branded NurOwn), missed all primary and secondary endpoints in its Phase 3 trial by a very wide margin. Given these results, FDA refused to file the company's biologics license application, but the company nonetheless filed over protest. At a recent advisory

committee meeting, FDA explained that in addition to failure on pre-specified endpoints, biomarker data did not provide evidence of NurOwn's clinical effect and there was a survival imbalance: more patients who received the drug died than those who received placebo. The agency also noted serious product quality deficiencies and manufacturing concerns, such that even if the product were effective, it was not clear the company could produce it consistently for future patients. The company pointed to additional analyses suggesting a possible treatment effect in some patients with earlier disease, but FDA statisticians explained that unplanned subgroup analyses have a "high risk of obtaining false positive results . . . and break randomization that may result in imbalance in measured and unmeasured baseline prognostic factors, which leads to confounding."[28] In other words, any benefit they show may not be real.

Ultimately, the advisory committee voted 17-1 (with 1 abstention) that the data presented did not demonstrate substantial evidence of effectiveness. Notably, the committee included a patient living with ALS, who voted with the majority against approval. In addition, the ALS Association (ALSA), the largest patient advocacy funder of BrainStorm's NurOwn program, declined to endorse the drug after the company refused to provide a full data package to undergo the Association's independent peer review process. ALSA explained that "[t]he amazing testimonials we have seen online do not align with the data that BrainStorm has shared with us or has been published in peer-reviewed publications."[29]

Last week, BrainStorm withdrew its NurOwn application and stated that it plans to conduct another Phase 3 trial to follow up on the exploratory subgroup analyses. Even though the drug remains unapproved, the company can use FDA's expanded access pathway to provide patients with NurOwn for treatment use while this next trial is being planned; it can also provide the drug via expanded access to patients who do not qualify for the trial once it is up and running. In addition, FDA allows recovery of direct costs for the provision of expanded access drugs[30,31] and there are other mechanisms for covering expanded access expenses specifically in the context of ALS.[10]

To some, NurOwn is the poster child for why the Promising Pathway Act is needed. A drug that may help some patients has not been able to meet the current statutory standard for

approval. But I think what the NurOwn example shows is just the opposite: the current approval standard must be maintained.[32] Even with all the flexibility that FDA has – and has shown in prior rare disease drug approvals, including for ALS – it could not find anything in the NurOwn data to hang its hat on because the evidence wasn't there. Why bother conducting efficacy trials simply to ignore their results? **Rare disease patients deserve better than to be treated like second-class citizens, sold drugs not even shown to be likely to work.**

It is certainly understandable for individual patients to be willing to risk substantial uncertainty for themselves before better evidence comes available, especially when they have no time to lose, and I support their right to do so via expanded access. However, **weakened approval standards affect all patients**. Sometimes I hear advocates seeking approval of a new drug say, "if other patients don't want to take it, they don't have to" – indeed, that's just what some have said about NurOwn. And it's true. But the issue is far more complex.

One of FDA's most important roles is to incentivize companies to produce information that patients and clinicians need to meaningfully guide their treatment decisions.[33] Under the Food, Drug, and Cosmetic Act, companies cannot sell their drugs – and therefore cannot profit – until they generate strong enough evidence to convince FDA the drug is safe and effective. As a result, companies seek to generate the evidence that FDA demands. If FDA demands less, patients and clinicians will have less, even if they really want and need more.

One must look only as far as the dietary supplement industry to see how this plays out. Unlike drugs, dietary supplements can be marketed without evidence of safety or effectiveness. As a result, we simply lack that evidence – and any meaningful innovation.[32] Imagine if what you had available to treat your life-threatening illness was rows and rows of products, none of which you knew worked. **More does not always mean better.**

This is especially true when we consider the opportunity costs. Even when there are no proven treatment options for a life-threatening disease, the choice about whether to try an uncertain drug has important tradeoffs. Side effects described as mild can cause substantial discomfort – is time spent dealing with diarrhea, nausea, headaches, extremely dry skin, or dry

mouth worth it for a drug that might not work? Surely for some, the answer will be yes. But how are others to make those decisions without information to guide them? Patients may also have to decide whether to incur hefty financial costs for an unproven drug – or whether to take a provisionally approved drug instead of enrolling in a trial of one that might be better. That latter choice is particularly salient because if patients seek unproven but approved drugs rather than choosing to participate in research to study new alternatives, it will be difficult to study those alternatives and improve the field. In this way, **weak FDA approval standards can entrench poor treatment options, leaving future patients no better off than patients today**.[1,5,8]

FDA's existing expansive regulatory flexibility raises many of these same concerns. However, **the response should not be to further weaken approval standards – at the very least, it should be to shore up the ability to collect rigorous, high-quality data after approval.**[2] Unfortunately, patient registries do not meet that bar. The Promising Pathway Act asks them to do more than they are capable of.

THE PROBLEM WITH PATIENT REGISTRIES

Because the Promising Pathway Act does not require any additional studies following provisional approval beyond a patient registry, and because it directs FDA to allow use of real world evidence to fulfill follow-up requirements and support applications, the bill appears to contemplate registry data serving as the exclusive support to move a drug from provisional to traditional approval. However, for several reasons, **registries are limited in their ability to demonstrate a drug's effectiveness, making this one of the most important concerns about the bill**.

Most importantly, **registries do not involve randomization or blinding, and they often lack a concurrent control group**. In addition, they often fail to include confounding patient and medical center variables that could influence outcomes.[34] Patients who are prescribed and choose to take a provisionally approved drug – the patients who would be followed under the Promising Pathway Act – are likely to be meaningfully different from those who do not. For example, they may be healthier or perhaps sicker, they may have different comorbidities, they may be taking

different concomitant medications, they may have different access to care, services, and treatment, and they may be more optimistic about a drug's likelihood of working. Similarly, physicians who prescribe a provisionally approved drug are likely to engage in treatment behaviors that differ from their non-prescribing colleagues. Patients who are enrolled in an open label trial in which they know they are receiving the active treatment of interest, and the physicians treating them, often report positive outcomes that can be difficult to evaluate. These challenges are exactly why randomized, blinded study designs are so valuable, even if observational data are available from patients who are not taking the drug of interest. **Randomization and blinding help make sure that the only difference between patients, including relevant differences that may be difficult to predict or measure, is whether they are receiving the investigational drug.** This, in turn, allows any differences in outcomes to be causally attributed to the drug.

Sometimes an external control group can address these challenges, for example relying on data collected from patients in the control group of an earlier study or natural history data for comparison. FDA has explained that "if the natural history of a disease is well-defined and the disease is known not to improve in the absence of an intervention or with available therapies," historical information can potentially serve as a control group, if available.[35] However, **when a disease is heterogenous with regard to its clinical presentation, severity, prognosis, speed of progression, and other factors, when its natural history is not well understood, and when a drug's effect size is likely only small or moderate, randomization is essential to proving whether a drug works**. Without it, the risk of bias and confounders is too great – in other words, it becomes impossible to know if it is the drug that caused the effect, or if it is one of the many other differences in background conditions between the patients.

Unfortunately, many rare diseases lack strong natural history studies and face the kind of heterogeneity within and across patients that makes reliance on external control groups unreliable. In ALS, for example, "plateaus and small reversals are common, especially over brief intervals," such that stable disease for a short period of time should not be interpreted as a treatment effect.[36] In contrast, large, sustained ALS reversals are rare – yet that type of large

drug benefit likely would be clear from an early phase trial and not just a registry, potentially supporting traditional rather than provisional approval.

To be clear, the type of real world data generated by registries can be important to tracking safety, evaluating the outcomes achieved for a wider range of patients facing a wider range of circumstances than are typically included in clinical trials, and gathering data over a longer period of time. Accordingly, I do not mean to suggest that registries are never helpful – they can be. In fact, because they can be specifically designed to collect certain types of information, they can be better sources of real world data than electronic health records (EHRs) and payer claims data, which are primarily intended for other uses and therefore may not be fit for purpose.[37] The problem is simply that – **even for rare diseases – registries typically cannot substitute for rigorous, prospective, randomized trials when we're trying to determine whether a drug in fact works**.

With that substantial limitation in mind, it is also important to be aware of two additional challenges facing registries. First, having distinct registries for individual drugs can prevent them from being used for important comparative effectiveness research due to differences in the data collected. A single unified registry with consistent data requirements would be most helpful. Second, registries rely on clinicians to input the relevant data during routine clinical practice, a time consuming and uncompensated task that can result in major gaps in data collection and quality. Registries linked to EHRs and claims data therefore can be preferable to any single source on its own, and registries required by payers are most likely to have complete data.

ADDITIONAL CONCERNS REGARDING THE PROMISING PATHWAY ACT

Although the most foundational concerns with the Promising Pathway Act are the dual concerns of weakened standards for approval and insufficient requirements to confirm benefit, the bill presents several additional issues:

- The bill proposes to shorten the time for FDA review of provisional approval applications to only 90 days. However, even if review occurs on a rolling basis, **90 days is likely not**

enough time for FDA's scientists to adequately assess the relevant data, including with regard to possible safety concerns. Drugs granted priority review designation must be reviewed within 6 months, a timeframe that already places tremendous pressure on reviewers, especially given numerous unfilled positions at FDA. Moreover, available evidence indicates that post-market safety events are more common for drugs that were approved near their regulatory deadline.[38,39]

- The bill discusses several ways that provisional approval could be rescinded or withdrawn, e.g., due to side effects or passing expiration dates. However, **it is not clear how a drug could move from provisional approval to traditional approval**. It appears the bill contemplates this happening as a result of real world evidence generated by the required registry, but that is insufficient, for the reasons noted above.

- Relatedly, **the bill would problematically require FDA to consider waiving requirements for adequate and well-controlled studies when deciding whether a provisionally approved drug should move to traditional approval**. This means a drug could move to traditional approval with substantial uncertainty about whether it works and for whom.

- The bill takes the Food, Drug, and Cosmetic Act's existing language regarding "substantial evidence" of effectiveness and instead uses that same language in the context of describing the evidence of safety needed to support provisional approval, resulting in text that is very difficult to parse. Specifically, the bill calls for "substantial evidence of *safety* for the drug, such that there is evidence . . . to evaluate the *safety* of the drug involved, on the basis of which it could fairly and responsibly be concluded that the drug will have the *effect* it purports or is represented to have . . . ." (emphasis added). However, **evidence regarding safety has nothing to do with whether the drug will have its purported effect**.

- The bill discusses provisional approval based on "scientifically substantiated surrogates," seemingly without recognizing that FDA can already grant accelerated approval (with more concrete post-market study requirements than a patient registry) based on these unvalidated surrogate endpoints.

- The bill notes that approved researchers and medical professionals may access registry data for public health research in a de-identified, aggregated manner. However, **it does not indicate who may be denied access and on what grounds**. For example, it may be important for sponsors developing competing drugs to have access to the data. In addition, aggregated data may obscure key insights that can only be seen through individual level data, which could also be de-identified. Payers should also have access to registry data to support their decisions about coverage of provisionally approved drugs.

- The bill assumes that provisional approval may be renewed up to 3 times, for a total of 8 years. However, it offers **no description of what will be needed to grant these renewals**.

- Although the bill acknowledges that provisional approval will be based on less certain evidence, it expects payers to cover provisionally approved drugs as they do drugs approved on traditional standards of evidence. For Medicare, which has only very limited ability to negotiate price under the Inflation Reduction Act, that would mean paying whatever price the sponsor sets, despite substantial uncertainty.

EFFORTS TO ADDRESS CHALLENGES IN RARE DISEASE DRUG DEVELOPMENT

Although the Promising Pathway Act is not the right way forward, there are a number of other opportunities to meaningfully improve rare disease drug development. **The most important of these are upstream from FDA**, including support for scientific advancement in understanding these diseases so that sponsors are able to target the right mechanisms and conduct trials that ask the right questions through the right designs most likely to identify drugs that work. **Too often, the problem facing rare disease patients is not that FDA is standing in the way of good drugs – but rather that there are no good drugs at all.**

In addition to the wide-ranging flexibility FDA already exercises in drug approval, it has also undertaken several initiatives to address scientific bottlenecks and regulatory barriers arising

in the rare disease context, especially over the past year. Importantly, FDA is making these changes within their existing statutory authority without legislative change. For example:

- FDA's **"Support for clinical Trials Advancing Rare disease Therapeutics" (START) program**, informally described as Operation Warp Speed for rare diseases,[40,41] will be piloted with companies developing gene therapies to address rare or serious pediatric diseases or drugs to treat rare neurodegenerative conditions. The Center for Biologics Evaluation and Research (CBER) and the Center for Drug Evaluation and Research (CDER) will each select 3 sponsors to begin the program in 2024. The companies will obtain frequent advice and ad hoc communication with FDA staff to address product-specific development issues, such as study design, choice of control group, and selection of patient population. The hypothesis is that speeding response times – and helping sponsors recognize when they should be asking questions – will speed drug development times and help avoid problems that could inhibit approval down the road, especially for sponsors with less FDA experience. In addition, CBER's director, Peter Marks, has encouraged accelerated approvals for biologics, sought to help companies address manufacturing challenges for biologics early in development, and acknowledged the need for flexibility around what trials will be feasible in rare disease.[40]

- As announced last fall, CBER and CDER established a **Rare Disease Endpoint Advancement (RDEA) Pilot Program** to support novel efficacy endpoint development for drugs to treat rare diseases, through close collaboration between FDA and sponsors.[42] The pilot will include sponsors with an "active investigational new drug (IND) or pre-IND for the rare disease, or sponsors who do not yet have an active development program but have, or are initiating, a natural history study where the proposed endpoint is intended to be studied."

- Early in 2023, FDA launched another pilot program, called **"Split Real Time Application Review" (STAR)**, which seeks to allow earlier patient access to therapies that address an unmet medical need by shortening the time from the date an application is submitted to the action date.[43] The program applies to supplemental drug and biologics applications proposing new uses of approved therapies to address unmet medical need when clinical evidence

indicates the drug may demonstrate substantial improvement over available therapies. FDA will begin to review data once it receives a Part 1 submission including, among other things, all components of the efficacy supplement except for final clinical study reports. The sponsor must then submit clinical study reports and integrated summaries of safety and effectiveness as a Part 2 submission within 3 months. Because FDA will begin reviewing the data sooner, decisions will ideally move more quickly. However, unlike the Promising Pathway Act, the STAR program does not change the relevant PDUFA date, the clock for which would start with the Part 2 submission, nor would it apply to products with no prior approvals.

Although each of these programs needs to be assessed following their pilots, they demonstrate FDA's efforts to be responsive to the needs of the rare disease community, especially when considered alongside the expansive exercise of regulatory flexibility described above.

In addition, FDA has developed a **5-year action plan for rare neurodegenerative diseases**, including ALS, which it published last year in response to a directive from the Accelerating Access to Critical Therapies for ALS Act, or "ACT for ALS."[44] ACT for ALS also directed grant funding for scientific research using data from expanded access to investigational ALS drugs; development of a public-private partnership for rare neurodegenerative diseases including both NIH and FDA; and an additional grant program focused on characterizing neurodegenerative diseases and their natural history, identifying molecular targets, and increasing the efficiency and productivity of clinical development of therapies.

As part of FDA's action plan, it developed an inter-center **Rare Neurodegenerative Diseases Task Force** intended to coordinate efforts toward advancing science and drug development for rare neurodegenerative diseases and developed an **ALS Science Strategy** to address challenges to ALS drug development. That strategy focuses on **improving characterization of ALS disease pathogenesis and natural history, facilitating access to clinical trials including through decentralized models, encouraging the incorporation of expanded access into clinical development programs, enhancing trial infrastructure and agility, facilitating data sharing, and exploring innovative trial designs including novel statistical approaches for small populations**. Note that each of these areas focuses attention on

improving the science rather than weaking approval standards, with the explicit intention that improvements in ALS science will also benefit other rare neurodegenerative diseases. A variety of other scientific efforts are also underway, including **NIH's Therapeutics for Rare and Neglected Diseases (TRND) Program**, which is leading an effort to screen existing compounds for potential repurposing to treat rare and neglected diseases and working to develop a "gene therapy toolbox" that can help address obstacles in manufacturing and delivery.[45]

CONCLUSION AND RECOMMENDATIONS

The terrible reality is that many patients, both children and adults, are facing serious and life-threatening diseases without good treatment options. However, that is not because FDA is blocking access or refusing to exercise its substantial flexibility to approve new drugs. Instead, it is because in too many areas, the science has not caught up to the need. **Addressing that scientific gap should be the focus of our attention.**

In the meantime, I recognize patients need both evidence and access. This committee might facilitate that goal in several ways:

1. **Ensuring funding both for rare disease drug research and efforts to promote clinical trial accessibility**, so that every patient who wants to participate in a clinical trial can do so.

2. **Supporting efforts to encourage the provision of investigational drugs to patients unable to participate in clinical trials through FDA's expanded access pathway.**[8]

3. **Clarifying that FDA has the authority to require post-market efficacy studies even for drugs approved outside the accelerated approval pathway, encouraging FDA to vigorously enforce post-market study requirements, and supporting FDA when it seeks to rescind approvals for drugs that fail to confirm benefit**. Importantly, these steps may ease agency concerns about granting early approvals in specific cases, adding flexibility.[2]

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Thank you for inviting me to testify and for your commitment and attention to these critical issues for all patients and families that are or will be affected by rare, serious diseases.

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