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Rare Diseases: Expediting Treatments for Patients

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Chairman Paul, Ranking Member Casey, and members of the Senate Subcommittee on Children and Families, I thank you for the opportunity to testify before you today, and for your interest in this important program and topic. I am honored to have this opportunity to advocate on behalf of children and families afflicted by rare diseases.

My name is Marc Patterson. I am a pediatric neurologist, and I currently serve as a Professor of Neurology, Pediatrics and Medical Genetics at Mayo Clinic in Rochester, Minnesota. Since my fellowship training at the National Institutes of Health almost 30 years ago, I have focused my practice, education and research on children and families with rare disorders, specifically inherited metabolic diseases. I have had the privilege of caring for many hundreds of children and families burdened by rare diseases, supporting them through service on advisory boards of lay foundations, by educating my peers and the public about these disorders, and by planning and executing clinical trials. I have come to admire the courage, creativity and resilience of these extraordinary American families; they are my personal heroes.

The Burden of Rare Diseases

Congress has recognized the plight of people with rare diseases for more than a generation. The Orphan Drug Act of 1983 (PL 97-414) provided needed incentives for researchers to devote resources to investigate and develop therapies for rare diseases affecting small patient populations, where otherwise the projected returns or risks of failure might have been overwhelming deterrents stifling innovation. The Rare Diseases Act of 2002 (PL 107-280) further strengthened interest in rare diseases at the National Institutes of Health. At the time the Rare Diseases Act was enacted, more than 6,000 such diseases affected approximately 25,000,000 US citizens. But each rare disease alone often did not have a sufficiently sized patient population to adequately interest prospective investigators. These acts of Congress are widely regarded as having been highly successful in stimulating the interest of industry in developing Orphan Drugs.

Advances in diagnostic techniques, particularly next generation sequencing of deoxyribose nucleic acid (DNA), have led to the rapid expansion of the number of recognized genetic diseases, a substantial proportion of which are described as ultra-rare. These disorders have typically been recognized in less than a thousand or so individuals, sometimes as few as 10 or 20. Rare and ultra-rare diseases individually affect relatively few people. But because there are so many of these disorders, they collectively affect a very significant proportion of the population, and constitute a national burden far in excess of their individual numbers. Few of these disorders have approved therapies, or, until recently, even the prospect of disease specific treatments. Most have multisystem manifestations, and the most severe forms

typically involve the nervous system, causing debilitating symptoms in varying combinations, including intellectual delays or dementia, impairment of speech language, hearing, vision, epileptic seizures and a variety of movement disorders, leading ultimately to complete dependence for activities of daily living, and premature death.

Although each family's story is unique, certain common themes emerge. The initial symptoms of rare and ultra-rare diseases are often non-specific in character, insidious in onset, and are often mistaken for those of more common disorders. Accurate diagnosis is typically delayed, often by years, sometimes by decades, as families travel from physician to physician and medical center to medical center, enduring extensive, expensive, and sometimes invasive, investigations, before the correct diagnosis is eventually made. By this time, symptoms are well established, and the opportunity for early and effective intervention has often passed, because irreversible tissue damage has occurred.

Once a diagnosis has been made, the affected individuals and their families have not reached the end of their journey, but simply enter a new, similarly exacting phase. They face incomprehension on the part of caregivers and the community, who are unfamiliar with the disease and its burdens, and a bureaucracy and rehabilitation system designed primarily to care for older adults with common diseases, not children and young adults with progressive disorders. Often families are told – inaccurately and inappropriately - that nothing can be done for their child. Thus, the burden of caring for a family member with profound disabilities is compounded by struggles with a system that erects barriers to care for the most innocent and

deserving of our citizens – children with rare and ultra-rare diseases. Disease modifying therapies are usually lacking, although the potential for such therapies is growing rapidly as the relevant science continues to advance.

Challenges in Developing Disease-modifying Therapies for Rare and Ultra-rare Diseases.

The process of developing new treatments – specifically pharmaceutical therapies – is a long and complex process, most often the product of discovery by academic scientists in the preclinical phase, with subsequent translation to an approved product in cooperation with an industry sponsor. The multiphase, stepwise process of studying potential therapies requires the participation of increasingly large numbers of subjects, ultimately in double blind, randomized, controlled clinical trials. This pathway is challenging, but feasible, for diseases in which the potential pool of clinical trial participants is measured in the thousands, and in which the assembly of cohorts of well-matched subjects is readily accomplished.

Industry sponsors are easier to identify for diseases with a potential market of thousands, or even millions, than for rare and ultra-rare disorders. For these diseases, the conventional pathway to drug approval raises hurdles that cannot be easily overcome, if at all. The potential pool of participants is small, and within that circumscribed group, not all individuals are willing participants or suitable candidates for clinical trials. Moreover, broad variability in the symptoms and signs of rare diseases, in the age at which they first present, and the rate at which they progress, may render the assembly of well-matched cohorts of patients for controlled trials impossible.

Another important factor that limits the applicability of the traditional clinical trial model to rare and ultra-rare diseases is the use of unapproved drugs or unstudied supplements in patients with these disease disorders. Parents are understandably desperate to explore any potential remedy for their child's illness, and when a drug that is a candidate for a clinical trial in the United States is available as an approved product in another country, or as a supplement here, parents will often import the drug, or administer the supplement –thus excluding the child as a candidate for a conventional clinical trial.

Another challenge is how to measure the effects of drugs in rare diseases. Ideally, clinical measures based on prospective natural history studies, validated biomarkers and surrogate biomarkers should be available to define clinically meaningful outcome measures. Such measures are usually lacking in rare and ultra-rare diseases, and assembling cohorts of patients to perform such studies has historically been difficult, owing to lack of funding support. The development of Rare Disease Clinical Research Networks with support from the National Institutes of Health, has a been a welcome development in addressing this deficiency. The establishment of The Therapeutics for Rare and Neglected Diseases (TRND) program, which is designed to facilitate the development of new therapeutics for rare and neglected diseases, represents another step forward. Still, neither of these advances has addressed the fundamental challenges in planning and executing clinical trials for rare and ultra-rare diseases.

Clinical trials are overseen by the Food and Drug Administration (FDA). The current framework for drug approval dates back to the Food, Drug and Cosmetic Act of 1938 (PL 75-717), which required that such agents be safe. Following the thalidomide disaster in the late 1950s, the Kefauver Harris Amendment of 1962 (PL 87-781) strengthened safety provisions, and added the requirement that manufacturers demonstrate the efficacy of drugs prior to approval. Neither this Act, nor many subsequent amendments to the Food, Drug and Cosmetics Act, has made specific provisions for the approval of drugs for children and adults with rare and ultra-rare diseases.

Recommendations to Accelerate the Approval of Drugs by the FDA to Treat Rare and Ultra-rare Diseases.

As the number of recognized rare and ultra-rare diseases continues to increase, and as precision medicine begins to dissect out the rare disorders which are currently contained within common syndromes, the need for better pathways to drug approval becomes increasingly urgent, and proactive legislation by Congress is critical.

I urge Congress to legislate specific pathways for the approval of drugs to treat rare and ultra-rare diseases. I suggest the following specific measures regarding drug approval for rare and ultra-rare diseases, to provide FDA regulators with a more refined set of tools to benefit this underserved population:

A. Require the FDA to accept alternative study designs that are better suited for these small, inhomogeneous, populations. These include, but are not limited to:

1. Adaptive trial designs, which allow for changes to made to the trial as it proceeds (Chow and Chang, 2008; Gupta, 2011; Cornu, et al 2013);
2. The use of Bayesian methods for the analysis of trial data (Hampson, et al 2014; Johnson, et al, 2009)
3. The use of trial designs that attract more participants by either guaranteeing access to the study drug for all participants, or ensuring more prolonged access to the study drug. Such designs include randomized placebo-phase, randomized withdrawal, early escape, stepped wedge and crossover trials (Gupta, et al 2011; Cornu, et al, 2013).
4. N-of-1 studies to address the type 2 errors that are frequent when the effects of drugs that fail to meet a predetermined level of statistical significance, owing to lack of power, usually owing to insufficient numbers of participants and large variation in outcome baseline measures. The N-of-1 trial design allows each participant to serve as his or her own control, permits multiple crossovers between placebo and active therapies, and provides data suitable for meta-analysis to make estimates of group effects (Gupta, et al 2011; Shamseer, et al 2016, Zucker, et al 2010). Recommendations for the standardization of N-of-1 trial reporting have been published (Vohra, et al 2015)

B. ***Require the FDA to accept the results of well-conducted clinical trials supervised by national regulatory agencies outside the United States, or by such agencies acting***

in concert with the FDA. By their nature, studies in rare and ultra-rare diseases include all willing and eligible subjects, and requiring that study populations be exclusively recruited from the United States in order to ensure broad representation of the US population, is neither feasible nor appropriate in these circumstances;

C. ***Require the FDA to work with lay groups, academic medicine, industry and other international regulatory agencies, to develop disease registries, ideally patient owned and managed, containing secure, professionally entered and patient/parent entered data, which will be used to enhance understanding of natural history, to develop outcome measures, and to support clinical trials.*** The International Niemann-Pick Disease Registry (INDR) is one such example of a collaborative, patient-initiated and owned venture (https://inpdr.org).

Current advances in the basic science of biology are leading to better understanding of disease mechanisms that hold great promise to alleviate the burden of rare and ultra-rare disease. I thank you for the opportunity to present these suggestions to the subcommittee, and urge Congress to provide regulators with a new, improved set of legislative tools to facilitate the translation of those advances to safe and effective medicines for the millions of Americans suffering from rare and ultra-rare diseases.

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