Testimony
of

Professor Mallory Factor

Before
Subcommittee on Children and Families Of
US Senate Committee on Health Education Labor and Pensions

Hearing on Development of Treatments for Rare, Genetic Diseases October 3, 2018

1. Chairman Paul, Ranking Member Casey and Distinguished Members of the Subcommittee, thank you for the opportunity to discuss the regulation of drug development for patients with rare genetic diseases.
2. My name is Mallory Factor and my statement is drawn upon my experience as Chairman of an orphan drug development company, IntraBio Inc., and our interactions with regulatory agencies in the United States and Europe on matters relating to our clinical development programs for orphan drugs. IntraBio was founded with the purpose of developing novel therapies for rare patient populations with genetic and neurodegenerative conditions, such as inherited Cerebellar Ataxia (e.g. Ataxia- Telangiectasia, Spinocerebellar Ataxias, and Ataxia with Ocular Motor Apraxia) and Lysosomal Storage Disorders like Tay-Sachs and Niemann-Pick Disease Type C, which are predominately fatal conditions and for which patients have extremely high, unmet medical needs.
3. Before founding IntraBio in 2015, I have advised numerous early stage companies over my 30-year career, including two medical devices companies.

Background

4. I am here today to share with you my observations on some of the obstacles that may delay and even restrict novel orphan therapies from getting to patients, and some ideas for how orphan drug developers and the Food and Drug Administration (FDA) could collaborate more closely to bring treatments for rare, genetic diseases to the point of approval so that they are made available to patients with conditions or diseases for which there is a high unmet medical need.

5. The FDA defines an "orphan drug" as a "drug intended to treat a condition affecting fewer than 200,000 persons in the United States, or which will not be profitable within 7 years following approval by the FDA." It is estimated there are over 7,000 rare ("orphan") diseases[1], a number of which are life-threatening, debilitating, and have patient populations much smaller than this standard, with numbers in the mere hundreds.
6. However, while the patient population for individual orphan diseases may be small, is estimated that in total, some 30 million Americans are affected by orphan diseases. For a large majority of these rare patient populations, there is no FDA approved therapy available to treat their condition.
7. A possible explanation for why a majority of orphan diseases do not have approved treatments is that the process for developing and getting marketing approval for orphan drugs is almost the same as for drugs with common, non-serious disorders.
8. In this pathway, there are several requirements for assessing the safety and effectiveness of a new drug. These are concerned with the need to: establish the compound's safety and tolerability profile; design feasible trials with clinically relevant outcome measurements that assess the clinical efficacy of a treatment; select the correct sample size and eligible patients; recruit trial subjects according to established ethical principles; and secure adequate resources and funds to execute the study and address the regulatory requirements.
9. In the case of rare diseases, which often have an ultra-small patient population where the diseases are rapidly progressive, a large clinical variability between patients, and fatal without treatment, traditional regulatory requirements can often become monumental challenges.
10. This is because, as for all drug development, orphan drug developers cannot feasibly conduct development programs without consent from expert clinicians and the patient community regarding the scientific and ethical rational of development programs. In addition, there must be consent from regulatory agencies regarding the appropriateness of the development programs for regulatory approval.
11. However, for orphan drugs, the traditional regulatory pathways for non-clinical and clinical development are less likely to be compatible with the scientific and ethical rational deemed

[1] The US defines an orphan condition based on disease incidence of less than 200,000 patients which would represent approximately 61 cases per 100,000 based on the current estimate of US population of 326 million.

appropriate by clinicians and the patient community. The process of getting all three bodies of experts—regulatory agencies, clinicians, and patient communities—to agree is often particularly time-consuming, expensive, and uniquely challenging for orphan drug developers.

12. Large pharmaceutical companies that have the resources to navigate the complex and costly orphan development process have traditionally had very little involvement, especially in the early stages, as rare disease therapeutics are assumed to have small markets and therefore small returns on investment.
13. Orphan drug development therefore relies on the province of startups or small companies who have significantly less resources and funding. However, due to the challenges of developing drugs for small patient populations with debilitating, fatal diseases, developing treatments for many orphan conditions is simply not economic.
14. For example, GM1 Gangliosidosis is a rare, genetic lysosomal storage disorder that predominately affects infants and early juveniles and is extremely debilitating, rapidly progressive, and has less than 200 known cases. Because the non-clinical and clinical requirements for novel GM1 therapies are the same as drugs for common, non-serious indications, these fixed long timelines and high costs cannot be justified due to the very-limited potential economic return.
15. The costs and difficulty of conducting trials for GM1 are even greater than for other conditions because it is a challenge to develop a clinical trial programs that accommodate the ultra-orphan patient population and rapidly progressive conditions, and also meet the regulatory "gold standards" for large, randomized, controlled trials.
16. Sadly, the unique challenges and costs of orphan drug development mean that too many promising treatments for orphan diseases are abandoned even before they are trialed in patients, as companies exhaust their resources or pivot to treating common diseases which can provide return on their investment.
17. While orphan drug developers are commercial ventures, their work on developing new treatments ultimately serves the patient communities. Anything that Congress can do to facilitate and encourage more efficient orphan drug development for these underserved patient populations should be done, of course bearing in mind the safety as well as the needs of the patients.

Current Problem, Proposed Solutions

18. To facilitate the development of orphan drugs, a new regulatory pathway which differs from the traditional development program is needed to expedite promising treatments into the hands of patients with rare genetic diseases is needed.
19. This pathway for the development and approval of treatments for rare genetic diseases should be designed so that there is earlier, more frequent interactions between the FDA and drug developers so that they are able to collaborate and design non-clinical and clinical programs that take into consideration the scientific and ethical considerations of clinicians and the patient community, such as the very small number of patients, the rapidly-progressive, debilitating nature of the diseases, the clinical variability between patients, and fact that there is no approved treatment, for a majority of rare, fatal genetic conditions, leaving patients with high unmet medical needs and desperate for treatment.
20. If these measures were implemented, I believe orphan drug development would become more efficient, as non-clinical and clinical development programs would be conducted that are appropriate for the patients being treated and considerate of the product-specific risk-benefit profile. As such, the much-needed orphan drugs would reach patients with rare, fatal, genetic diseases faster while maintaining the high standards for safety.

Challenges: Orphan Drug Act and Breakthrough Therapy Designation are not sufficient

21. Due to these unique challenges, as well as long timelines, and high costs of development, rare disease therapies are assumed to have small markets and thus development of treatment for orphan conditions are generally considered to provide insufficient economic incentives for developers, given the limited potential return on investment.
22. In light of this, Orphan Drug Act/Designation was put in place to aid and encourage the development of drugs for rare diseases. The Orphan Drug Act was a pioneer legislation that has aided in in helping new treatments get to patients: before the legislation was

enacted in 1983, only 38 orphan drugs had been approved; by 2014, 468 indication designations covering 373 drugs have been approved. [2]

23. However, the orphan drug act has not entirely solved the problem, as the proportion of orphan drugs approved today is disproportionately smaller than the number of non-orphan drugs approved. A plausible explanation for this difference is that a majority of the benefits of the Orphan Drug Act are not triggered until after clinical trials have already been conducted and New Drug Approval (NDA) is sought through which drug developers formally propose that the FDA approve a new pharmaceutical product.
24. Similarly, designations like "Breakthrough Therapy Designation" are granted too late in the development process, only after Investigational New Drug (IND) applications for clinical trials are filed. As a consequence, the interaction between orphan drug developers and the FDA is significantly limited throughout the early research stage and while designing clinical trials.
25. Since orphan drug development still predominantly relies on the province of startups or small companies that have significantly less resources and funding than Big Pharma, these provisions therefore do not actually help orphan drug developers bring new treatments through the trial approval process.
26. In the absence of early and frequent contact and collaboration between orphan drug developers and the FDA, novel therapies often fail orphan drug developers face too much uncertainty in designing non-clinical and clinical programs that satisfy patients, clinicians, as well as regulatory requirements, and thus many valuable treatments never become available to address the extremely high unmet medical need.

Proposed Solutions: Earlier and Greater Consultation with the FDA

27. New legislation which introduces benefits of orphan designation earlier in the development process, such as specific programs to enhance closer and greater early engagement with FDA, would enable drug developers consult the FDA about the acceptability of their non-

[2] Hadjivasiliou, Andreas (October 2014), "Orphan Drug Report 2014" (PDF), *EvaluatePharma*, retrieved 28 June 2015

clinical data, trial design, and endpoint assessments early and frequently in the development process and to deploy limited resources more effectively.

28. The FDA has flexibility to decide on the approvability of a new treatment, including the required non-clinical profile, as well as the appropriateness of the "gold-standard" randomized controlled trial. This flexibility can greatly benefit rare disease patients if it is applied early and throughout both the non-clinical and clinical development process for orphan drugs.
29. Greater interaction between the FDA and orphan drug developers from an early stage in the drug development and market approval process would provide regulators with more complete scientific and ethical background of the risk-benefit of a proposed treatment. Given this "whole picture" view, regulators could exercise this flexibility in regard to both non-clinical and clinical programs based on what is already known about the pharmacological properties of the orphan drug and the patient population it intends to treat.
30. Regulators would be able to identify what data is relevant and must be generated before trials can be approved—and leave aside other requests for additional data that would be nice to have but is not necessarily critical to the overall benefit/risk assessment.
31. Early and frequent interactions between orphan drug developers and the FDA also reduces the guesswork about what is acceptable in terms trial designs and assessment endpoints and realistic to achieve given the demographics of the patient population.
32. Early, frequent interaction would help ensure that cost-effective nonclinical development programs, ethical trial design, and appropriate clinical outcomes for patients with fatal, rapidly progressive, rare diseases are being used. This would make orphan drug development a much more expedited and streamlined process so that new treatments would reach and benefit patients sooner.

Case Study—IntraBio

33. IntraBio is a small biopharmaceutical company whose mission is to advance patients' interest, and to develop novel therapies to treat fatal, rare, rapidly progressive genetic diseases with high unmet medical needs.
34. The company is developing a compound, N-Acetyl-Leucine, which is supported by both animal studies and numerous compassionate use studies in patients to be a potential

treatment for both rare genetic disorders like inherited Cerebellar Ataxia (eg Ataxia-Telangiectasia, Spinocerebellar Ataxias, and Ataxia with Ocular motor Apraxia) Tay-Sachs disease and Niemann-Pick disease Type C (NPC) as well as common neurodegenerative diseases like Lewi Body Dementia and Parkinson's disease. Given the extreme medical need, IntraBio is prioritizing the development of N-Acetyl-Leucine for the treatment of rare, genetic diseases (Tay-Sachs, NPC, and inherited cerebellar ataxia subtypes) which predominately affect pediatric patients and are fatal, rapidly progressive, display a huge range of debilitating neurological and physical symptoms, and have no treatments medically available.

35. IntraBio has commissioned further safety pharmacology studies to characterize the safety profile and further non-clinical studies to investigate the optimal form and mode of administration for patients.
36. This data forms a good scientific basis for IntraBio to advance research and development with N-Acetyl-L-Leucine. IntraBio's objective is to conduct clinical programs as efficiently as possible by taking full account of what is already known about the active pharmaceutical substance and the demographics of the patient populations it intends to treat so to design clinical trials that are appropriate to study the clinically meaningful effects of the drug.
37. Medical need for these conditions is extremely high: Patient groups are asking for the drug to be available in the US and for trials to commence in the US to bring possible relief to terminal patients who are very young.
38. However, although orphan drug designation has been given to N-Acetyl-L-Leucine by the FDA for various conditions, this designation has not expedited the regulatory process, or increased the level of engagement with the FDA, which would have facilitated clinical development.
39. Because of limited interaction with regulators, a large degree of uncertainty remains around the implementation of trial designs and primary endpoints that would be adequate and appropriate for the patient populations intended to be treated with N-Acetyl-L-Leucine. This uncertainty remains despite the fact that the trial design, including the chosen endpoints to assess clinical effectiveness, is based on extensive input from the world

leading clinical experts specializing in treating these patients and conducting clinical trials in these diseases, as well as patient advocates representing the patient communities.

40. In our view, regular engagement between orphan drug developers and the FDA would allow regulators to get a full picture of the scientific rational behind the design of non-clinical and clinical programs for N-Acetyl-L-Leucine, and significantly expedite the regulatory process, making the development process more feasible and cost-effect, and getting treatments to patients faster.