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RARE DISEASES: EXPEDITING TREATMENTS FOR PATIENTS

HEARING

BEFORE THE

SUBCOMMITTEE ON CHILDREN AND FAMILIES

OF THE

COMMITTEE ON HEALTH, EDUCATION, LABOR, AND PENSIONS

UNITED STATES SENATE

ONE HUNDRED FIFTEENTH CONGRESS

SECOND SESSION

ON

EXAMINING RARE DISEASES, FOCUSING ON EXPEDITING TREATMENTS FOR PATIENTS

OCTOBER 3, 2018

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C O N T E N T S

STATEMENTS

WEDNESDAY, OCTOBER 3, 2018

RARE DISEASES: EXPEDITING TREATMENTS FOR PATIENTS

Wednesday, October 3, 2018

U.S. SENATE,
SUBCOMMITTEE ON CHILDREN AND FAMILIES,
COMMITTEE ON HEALTH, EDUCATION, LABOR, AND PENSIONS,
Washington, DC.

The Subcommittee met, pursuant to notice, at 2:31 p.m. in room SD–430, Dirksen Senate Office Building, Hon. Rand Paul, Chairman of the Subcommittee, presiding.

Present: Senators Paul [presiding], Cassidy, Alexander, Casey, and Hassan.

OPENING STATEMENT OF SENATOR PAUL

Chairman PAUL. I will call this Subcommittee to order.

We are a Subcommittee from the general Committee of Health, Education, Labor, and Pensions. We are here today to have a hearing entitled, "Rare Diseases: Expediting Treatments for Patients." I will begin with an opening statement before we introduce the panel.

Through our hearing today, I intend to examine regulatory barriers to entry for drugs that treat rare diseases, also known as orphan drugs. The F.D.A. defines orphan diseases as those with fewer than 200,000 patients.

There are over 7,000 conditions that science has identified affecting nearly 30 million patients just in the U.S. Unfortunately, about 90 percent of these are serious or life-threatening conditions, and most have no F.D.A. approved treatment.

The standard of approval for orphan drugs is similar, if not the same, as those for more common conditions. It can take upwards of a decade, sometimes, for a drug to make it from the bench to bedside, and costs can be upwards of $2 billion.

For terminal patients waiting for the cure that may never come, or one that comes too late, is simply not an option. Therefore, families and patients often resort to importation of drugs approved overseas, off label use, or may turn to dangerous chemical grade products.

As a physician, I understand how rare diseases affect the body and manifest themselves through devastating and debilitating symptoms. Even in my family alone, I have a nephew who has Neurofibromatosis 2 and we have had to deal with a disease that is not very common and many people have not seen, even many physicians have not seen.

As a parent, I can only imagine, though, the overwhelming desperation and hopelessness of being confronted with a fatal diagnosis and being told to simply enjoy the remaining time that their child has left.

To the extent that government can improve efficiencies to speed access to treatments for patients and families facing such a situation, such action should be taken without delay.

Despite providing the F.D.A. with numerous tools to expedite approvals, and continually increasing resources, review times have not decreased. Over the life of the current User Fee Agreement, the F.D.A. will take in more than $4 billion in user fees from the drug industry, amounting to over 70 percent of the agency's review budget for these products.

Since the beginning of my time in the Senate, I have worked to ensure that the F.D.A. has had the authority to accept data from foreign countries. Yet, despite these efforts, duplicative trials and testing are still required in order to bring most drugs to market.

In addition, drugs approved in Europe are not harmonized with the F.D.A.'s process, causing problems in an increasingly globalized scientific community.

I hope we can work together today, and in the future, to find solutions that work to expedite treatment for these patients.

With that, I would like to recognize the Ranking Member, Senator Casey.

OPENING STATEMENT OF SENATOR CASEY

Senator CASEY. Thank you, Chairman Paul, for calling this important hearing.

I want to thank the witnesses for being here and thank the Chairman of our Committee, Senator Alexander, for his presence here.

I wanted to apologize in advance. I have to leave in about 20 minutes. This hearing was scheduled at a time when I had a conflict. I wish that had not happened, but it did, so I have to leave early.

I will be submitting questions in writing for the witnesses and I look forward to your responses.

We are here today to talk about a critically important issue: the development of drugs to treat rare diseases. Thirty-five years ago, Congress passed the landmark Orphan Drug Act. This legislation represented the first concerted Federal effort to incentivize the development of new treatments specifically for rare diseases.

The Orphan Drug Act established grants to assist in the development of new orphan drugs. It established the Orphan Drug Tax Credit to further offset the research and development costs, and provided a longer period of exclusivity, a full 7 years, for orphan drugs.

As a result of the Act, over 600 orphan drugs have been approved and many more are in development. This compares to just 34 orphan drugs approved in the 15 years before the Act was in effect.

In recent years, Congress has taken a number of additional steps to streamline and speed up the development of new therapies for rare diseases. The first I will mention is one that I am quite proud of because I developed this policy with Senator Isakson.

This incentive is the Pediatric Rare Disease Priority Review Voucher Program, which rewards the development of a drug for a rare, pediatric disease with a voucher that can be used to give another drug priority review by the F.D.A., cutting the review time from 8 months to 6 months. Companies can keep the voucher to use it for another drug in their portfolio, and they can sell it and reinvest it in their own research.

I am grateful for the work of Senator Isakson on this with me.

Since the Pediatric Rare Disease Priority Review Voucher Program was established in 2012, 13 vouchers have been awarded for new drugs to treat rare pediatric diseases, for diseases ranging from cancer to a genetic cause of blindness to the first marijuana-derived cannabidiol drug to treat two rare forms of epilepsy.

The F.D.A. has a number of other tools at its disposal to aid in the development and approval of drugs for rare diseases, several of which have been enacted in the last two years. The same law that extended and strengthened the Pediatric Priority Review Voucher Program, the 21st Century Cures Act, also required the F.D.A. to develop guidance on how to use adaptive trial designs, a Bayesian method for clinical trials. The F.D.A. published the draft version of that guidance last month.

The same day, the F.D.A. also published guidance on the so-called Master Protocols which can allow a single clinical trial to evaluate multiple drug candidates, multiple disease types, and more than one patient population under the same clinical trial structure, potentially reducing the time and cost of generating the necessary data for approval.

One of the common points we hear from the patient community, and the companies working to develop new drugs, is that patients are, and understandably so, desperate for access to new drugs when it is hard to enroll them in clinical trials.

Congress has given the F.D.A. specific authority in the F.D.A. Reauthorization Act to consider ways to design clinical trials that incorporate data from expanded access use of investigational drugs.

The F.D.A. is also learning from the adaptive trial designs employed during the Ebola outbreak in 2014 and using those lessons to inform other clinical trials where the standard randomized, double-blind, placebo trial is not possible or is not ethical.

The agency has noted that these new study designs are relevant to the growing field of gene therapy and thus also to the rare disease community where so many of the diseases are genetic in origin.

I look forward to continuing to work with the patient community, other stakeholders, and Members of the Committee to advance drug development for rare diseases, while continuing to ensure patients can trust their drugs and trust that those drugs are both safe and effective.

Thank you very much.

Chairman PAUL. I would like to recognize the Chairman, Senator Alexander.

The CHAIRMAN. Thank you, Mr. Chairman.

I would like to thank the witnesses for coming. We look forward to this.

Senator Paul and Senator Casey have been real leaders in our efforts to put a spotlight on rare disease. I want to thank Senator Paul for the hearing. I want to thank Senator Casey for his work over the years, his contributions to the 21st Century Cures Act, as was Senator Paul. I look forward to the testimony.

We have a vote. I am managing the opioid bill on the floor with the votes at 3:15, so I will have to leave a little before that, but I look forward to the hearing. I salute Senators Paul and Casey for their focus on such an important topic.

Chairman PAUL. Well, thank you both for coming.

As you will see, if you have not been to a hearing before, we have multiple hearings going on everywhere around, as well as votes on the floor. So sometimes you will see people come and go, but I do thank Senator Casey and Senator Alexander for coming.

We are going to start with testimony from Mark Dant, who is the Chairman of the EveryLife Foundation for Rare Diseases, and also from the great Commonwealth of Kentucky.

STATEMENT OF MARK DANT, CHAIRMAN, EVERYLIFE FOUNDATION FOR RARE DISEASES, LOUISVILLE, KY

Mr. DANT. Chairman Paul, Chairman Alexander, Ranking Member Casey, and distinguished Members of the HELP Committee.

I am Mark Dant. I am the Chairman of the Board of the EveryLife Foundation for Rare Diseases and the parent of a child with a rare disease. The EveryLife Foundation is a science-based advocacy organization that works to bring lifesaving treatments to the 30 million Americans with rare diseases.

We represent the one in ten Americans affected by more than 7,000 known rare diseases with 50 percent of the rare disease patients being children many of whom will not live to see their fifth birthday. It is imperative that we significantly increase the number of F.D.A. approved rare disease treatments now.

My son Ryan was diagnosed at three years old with MPS-I, a rare lysosomal storage disorder. The cells in Ryan's body lacked a crucial enzyme that it needed to break down sugar. The hospital told us that children with MPS-I rarely, if ever, lived past their teens as there was no treatment for his disorder.

Because MPS-I was so rare, affecting only a few thousand children around the world, drug companies were not interested in funding the research. My wife, Jeanne, and I were told there would be little other that we could do for Ryan other than take him home and love him for as long as he lived.

I refused to accept the recommendations and I spent all my spare time trying to understand Ryan's condition. After a year my wife, Jeanne, and I founded the Ryan Foundation to raise money to find a treatment for MPS in time for our son Ryan. Our first fundraiser was a bake sale that netted $342.

Eventually, I learned of a pediatric researcher who was working to find treatments for children with MPS, Dr. Emil Kakkis, at Harbor UCLA. It was 11 years after the passage of the Orphan Drug Act, yet Dr. Kakkis had no funding for research.

Over the next several years, the all-volunteer Ryan Foundation raised more than $1 million for Dr. Kakkis' work, which culminated in a new drug therapy. This therapy would never have

come to fruition without the formation of a small biotech company, which pulled Ryan's drug through the pipeline in time to help him survive.

Rare disease absolutely needs biotech partners. Family organizations like my own simply do not have the capital necessary to bring treatments to approval.

In 2003, the F.D.A. approved Aldurazyme for the treatment of MPS-I, five years after Ryan and nine other children began a trail at UCLA.

Enzyme replacement therapy later turned out to be instrumental in treating several other previously untreated and devastating disorders, proving again that biotech involvement in one disorder leads to not one, but countless more disease treatments.

Ryan is now 30 years old, a graduate of the University of Louisville, and is the longest treated person with MPS-I in the world. Unfortunately, Ryan's story is the exception.

We are now 35 years since the Orphan Drug Act was signed into law, yet fewer than 400 of the 7,000-plus known rare diseases have F.D.A. approved treatments.

We call on Congress to close the innovation gap for the 95 percent of rare diseases that have no treatment by incentivizing companies to repurpose already approved drugs for rare disease. Many patients are using drugs off label including my own son Ryan. Drugs used off label do not have the appropriate safety, efficacy, and dosing information. They also lack coverage for the cost of the drug, as many insurers will not pay for off label use.

The bipartisan OPEN ACT, S. 1509, introduced by Senators Hatch and Menendez, is a patient-driven solution supported by more than 300 organizations, including my own, modeled after the bipartisan Best Pharmaceuticals for Children Act, which resulted in over 600 labeling changes.

The OPEN ACT has the potential to double the number of F.D.A. approved therapies for rare disease patients, and at a lower average cost than current rare disease treatments.

I urge Congress to pass the OPEN ACT before the end of this year. In addition, we call on Congress to do the following steps:

Fund a Center of Excellence for rare diseases;

Allow innovators to use novel biomarkers for rare disease research;

Shorten the seven years it takes to obtain an accurate diagnosis;

Pass the Newborn Screening Saves Lives Act; and,

Pass legislation to ensure coverage of de novo sequencing.

In conclusion, I ask all of you gathered here today—Republicans, Democrats, Independents—to please put your policies and politics aside and join the *rare* party. The F.D.A. is not our enemy. Biotech companies are not our enemy. Our enemies are the rare diseases that steal livelihoods, mobility, vision, minds, and in the worse cases, lives.

All of us, patients, policymakers, innovators must work together to speed the development of, and access to, safe and effective treatments for the rare disease patients across the Nation.

Thank you.

[The prepared statement of Mr. Dant follows:]

PREPARED STATEMENT OF MARK DANT

Chairman Paul, Ranking Member Casey and distinguished Members of the Senate Health, Education, Labor, and Pensions Committee. I am privileged to be here today to present my perspective as the parent of a child with a rare disease, and to represent the 1 in 10 Americans affected by the more than 7,000 known rare diseases. I serve as chairman of the board of the EveryLife Foundation for Rare Diseases, a science-based advocacy organization that works to bring lifesaving treatments to the 30 million Americans with rare diseases. There are more Americans who live with a rare disease than those who have HIV, heart disease, or stroke combined. 50 percent of rare disease patients are children, many of whom will not live to see their fifth birthday. Only 5 percent of rare diseases have FDA-approved treatments.

When my son Ryan was 3 years old, he was diagnosed with MPS 1—a rare lysosomal storage disorder. The cells in Ryan's body lacked a crucial enzyme they needed to break down sugar. The geneticist at Dallas Children's Hospital told us that children with MPS 1 almost never lived past their teens, as there was no treatment for his disorder. Because MPS I was so rare, affecting only a few thousand children around the world, drug companies were not interested in funding the research. My wife Jeanne and I were told there were no options other than to take Ryan home and love him for as long as he lived.

I refused to accept the doctor's recommendations. Despite working the night shift after recently being promoted to Lieutenant in the Carrollton, Texas Police Department, I spent all my off-duty time trying to understand Ryan's condition. After a year of lying on the floor next to our son's bed at night and crying, my wife Jeanne and I founded a non-profit called the Ryan Foundation to raise money to find a treatment for MPS in time for our son. Our first fundraiser was a bake sale that netted $342. After several years of going door-to-door asking for donations and a series of conversations with leading scientists across the United States and Europe, I was told about a pediatric researcher who was working to find treatments for children with MPS 1: Dr. Emil Kakkis at Harbor UCLA. It was late 1994, 11 years after the passage of the Orphan Drug Act, yet Dr. Kakkis had no funding for his research and was working out of a one-story World War II era bungalow behind the county hospital in Torrance, California in a lab he'd constructed with the help of his own family members.

Over the course of the next several years, the all-volunteer Ryan Foundation managed to raise more than $1 million for Dr. Kakkis' work on MPS 1, which culminated in a new drug therapy. This therapy would never have come to fruition in enough time for Ryan without the formation of a small biotech company, which pulled Ryan's drug through the pipeline in time for him to survive. Rare disease absolutely needs biotech partners. Family organizations simply do not have the capital necessary to bring treatments to approval. There are simply not enough companies to bring science already available to approved therapies.

In 2003, the FDA approved Aldurazyme for the treatment of MPS I—five years after Ryan and nine other children began the trial at UCLA. Enzyme Replacement Therapy later turned out to be instrumental in treating several other previously untreated and devastating disorders, proving again that biotech involvement in one disorder leads to not one, but countless more rare disease treatments.

Ryan is now 30 years old and the longest treated MPS I person in the world. Unfortunately, Ryan's story is the exception. So many parents hope to be able to find the right experts and raise enough money in time to save their children, but most of them will not be as lucky as we were.

We are now 35 years since the Orphan Drug Act was signed into law, yet fewer than 400 of the 7,000 plus known rare diseases have FDA-approved treatments. We know from our work on Aldurazyme that it is possible to generate the commitments needed to bring rare disease drugs through the development process. It is often even faster and simpler to repurpose existing therapies for rare disease indications. We must incentivize industry to invest in rare disease therapies and to repurpose existing therapies for rare disease indications.

We call on Congress to help **close the innovation gap** for the 95 percent of rare diseases that have no treatment by incentivizing companies to *repurpose* already approved drugs for Rare Diseases. Many patients are using drugs off-label; including my own son Ryan. Even rare disease patients who are fortunate enough to be treated with an FDA-approved therapy have multiple unmet needs that continue to alter their ability to live life without the pain and disability typically associated with their rare disease. Drugs used off-label to meet these needs do not have the appro-

priate safety, efficacy, and dosing information. They also often lack coverage for the cost of the drugs, as many insurers will not pay for off-label use. The bipartisan OPEN ACT (S. 1509), introduced by Senators Orrin Hatch (R-UT) and Robert Menendez (D-NJ), is a patient-driven legislative solution supported by more than 300 rare disease patient organizations. Modeled after the bipartisan Best Pharmaceuticals for Children Act of 2002, which resulted in over 600 labeling changes and provided substantial clinical data on drug safety and efficacy in pediatric populations, the OPEN ACT has the potential to double the number of FDA-approved therapies for rare disease patients at a lower average cost than current rare disease drugs. I urge Congress pass the OPEN ACT before the end of this year.

I also ask Congress to fund a *Center of Excellence for Rare Diseases and more specialized review divisions at the Food and Drug Administration*. The FDA must have specialized personnel who understand the complexity of rare disease drug development to allow more flexible clinical trial designs, such as an "allcomers" trial that will allow our very small, heterogeneous patient populations to participate. Additionally, rare diseases still do not have access to the Accelerated Approval Pathway as novel biomarkers for rare diseases are not accepted as endpoints. **Allowing the use of a biomarker as a surrogate endpoint will lower the cost of rare disease drug development by 62 percent**. Ensuring that the FDA has the expertise and understanding needed for rare disease trial design will help de-risk the regulatory process and encourage investment in ultra-rare diseases.

Finally, I ask Congress to seek policy solutions to alleviate the devastating diagnostic odyssey for our community. For a rare disease patient, the diagnostic odyssey, or the time it takes for an individual to be accurately diagnosed, is about 7 years. This is unacceptable. The devastating effects of many diseases are irreversible. Early diagnosis is critical to ensure patients have access to clinical trials and lifesaving therapies. Congress must reauthorize the Newborn Screening Saves Lives Act before it expires on Sept. 30, 2019. Additionally, the Senate should introduce companion legislation to the House's Precision Medicine Act to help mitigate and eventually end the diagnostic odyssey so many patients and their families endure. 80 percent of rare diseases are genetically based so coverage for genomic sequencing is critical.

I ask all of you gathered here today—Republicans, Democrats, Independents—please put your politics aside and join the *rare* party. I have spoken to countless rare disease families like my own across the country and their message is the same: Drug companies are not the enemy, nor is the FDA. Our enemies are the rare diseases that steal livelihoods, mobility, vision, minds, and in the most devastating cases—lives.

I work with many parents who have raised the money to develop the science, yet no drug company is interested in developing the treatment. My advice is for them is to start their own drug company. However, I ask you: Should that also be their burden? We need Congress to incentivize drug companies and innovators to partner with us to bring lifesaving treatments to patients before it's too late.

I have personally felt the pain of finding no hope because a rare disease has stolen the promise of our tomorrows. I have attended countless funerals of children who lost their battle to a rare disease and witnessed the pain in their parents as they say goodbye. We must work together to change our system to increase the speed of safe and effective treatments from the scientific bench to the bedside by removing the barriers to novel trial designs. We must consider the heterogeneity of ultra-rare diseases and understand the true value of "all comer trials" so that our small patient populations are no longer overlooked, and the value of their data understood. Treatments come from the partnership of patients, science, industry, and the FDA.

Our children's lives depend on it.

Chairman PAUL. Well put. Thank you for your testimony.

Our next witness is Dr. Marc Patterson, who is a Professor of Neurology, Pediatrics, and Medical Genetics at the Mayo Clinic.

STATEMENT OF MARC PATTERSON, M.D., PROFESSOR OF NEUROLOGY, PEDIATRICS, AND MEDICAL GENETICS, MAYO CLINIC, ROCHESTER, MN

Dr. PATTERSON. Chairman Alexander, Chairman Paul, Ranking Member Casey, and Members of the Committee.

I wish to thank you for the opportunity to testify before you today, for your interest in this important topic, and the work that you have already done. 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 the Mayo Clinic in Rochester, Minnesota.

I completed my fellowship training in rare diseases at the National Institutes of Health some three decades ago, and I have dedicated my career to children and families with rare disorders since that time.

I have cared for many hundreds of children and families. As you can gather from the testimony of the previous speaker, you can understand why I admire the courage, the creativity, and resilience of these extraordinary families who are my personal heroes.

Congress has recognized the plight of people with rare diseases for more than a generation to provide needed incentives for researchers to devote resources to investigate and develop therapies for rare diseases; and strengthen interest in rare diseases at the National Institutes of Health; and to encourage the Food and Drug Administration.

These acts of Congress are widely regarded as having been highly successful in stimulating the interest of industry in developing orphan drugs, and I thank Congress for that work and the work that you have done in furthering those ends.

I would like to emphasize the fact that advances in diagnostic techniques, particularly the next generation sequencing of DNA, have led to the rapid expansion of the number of recognized rare and ultra rare diseases; by which I mean, diseases that affect fewer than 2,000 individuals, sometimes as few as 10 or 20.

Collectively, these diseases affect a very significant proportion of the population, as you have heard, yet few of them have approved therapies.

Moreover, the increasing use of next generation sequencing means that disorders, which we currently think of as common diseases, will likely prove to be families of rare disorders in the future. So I think there is considerable urgency in finding better ways to develop treatments more rapidly.

As you already gathered from Mark Dant's testimony, every family's story is unique, but there are certain common themes.

The initial symptoms of rare and ultra rare diseases are often mistaken for those of more common disorders. Families will travel from physician to physician, from medical center to medical center enduring extensive, expensive, and sometimes invasive investigations before the correct diagnosis is eventually made. And often, that diagnosis is delayed by years. By this time, the opportunity for early and effective intervention has often passed.

The patient and their families then enter a new, and equally frustrating, stage like those caregivers and others who are unfamiliar, sometimes even with the name, let alone with the burdens of such a diagnosis. And they have to deal with a bureaucracy, which is largely designed to care for adults with common diseases, not children and young adults who have progressive disorders. Often, families are told, inappropriately, that nothing can be done for their child.

The process of developing any new treatments, specifically pharmaceutical therapies, is long and complex. Typically, this process requires large numbers of subjects, who will ultimately participate, as we have heard, in randomized, double-blind, placebo-controlled clinical trials. But this pathway is inappropriate and has many barriers for rare and ultra rare diseases.

As we have already heard, there is a small potential pool of participants. Not all individuals are suitable candidates who are willing to participate, and there is wide, individual variation from individual to individual in terms of the symptoms, the age of onset, and the rate at which the disease progresses. All of this makes the assembly of well-matched cohorts of patients for controlled trials well nigh impossible.

Another challenge is how to measure the effects of drugs in rare diseases because traditional measures are usually lacking.

While there have been many attempts to address these deficiencies, and there has been progress at the F.D.A. and the N.I.H., there are still fundamental challenges remaining.

The bottom line is that we need more effective methods and pathways for drug approval for rare and ultra rare diseases. I suggest that Congress and the administration consider a variety of approaches, a few of which I describe in my written testimony and which I will highlight now. I had three themes:

One is trial design, which Senator Casey has already addressed.

The second is the use of data from outside studies.

Finally, I would like to address the issue of registries.

First of all, I think that we should ensure that the F.D.A. will accept alternative study designs including adaptive trial designs and Bayesian trial designs, which have been mentioned, and ensure that patients will have access to the study drug to encourage participation.

Secondly, the F.D.A. should be required 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 F.D.A.

Finally, we should require the F.D.A. to work with family groups, academic medicine, industry, and other international regulatory agencies to develop disease registries, which contain secure patient and parent entered data, which can be used to enhance understanding of natural history to develop outcome measures and to support clinical trials.

I thank you for the opportunity to present these suggestions to the Subcommittee, and I urge Congress to consider providing regulators with a new, improved set of tools to ensure the translation of scientific and technological advances to safe and effective medi-

cines for the millions of Americans suffering from rare and ultra rare diseases.

I look forward to answering any questions you may have.

Thank you.

[The prepared statement of Dr. Patterson follows:]

PREPARED STATEMENT OF MARC C. PATTERSON

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 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 1950's, 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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Chairman PAUL. Thank you, Dr. Patterson, for your testimony and also for your lifelong work in trying to find cures for these awful diseases.

Our next witness is Dr. Michael Strupp, who is a Professor of Neurology at the University of Munich. When you conclude your testimony, if you want to introduce and show a couple of videos right at the end of your testimony, we would love to see the videos.

STATEMENT OF MICHAEL STRUPP, M.D., PROFESSOR OF NEUROLOGY, UNIVERSITY OF MUNICH, MUNICH, DE

Dr. STRUPP. Senator Paul, Senator Casey, Senator Alexander, and Senator Cassidy.

Thank you for the opportunity to present our suggestions. In my statement, I am going to focus on four topics:

First, what is meant by ultra rare diseases?

Secondly, what are the specific problems in such diseases in terms of designing and performing a clinical trial to get approval?

Third, what would be the impact of an adopted approval process on research and even investments by pharmaceutical companies?

Fourth and finally, my vision.

What does rare and ultra rare mean? Senator Paul already mentioned that rare diseases are defined by fewer than 200,000 people affected by a certain disease in the U.S. If you take into consideration a population of 325 million Americans, you will end up with a prevalence of less than 60 in 100,000.

There are, however, ultra rare diseases with a prevalence of less than a hundredth of that. Two examples are Niemann-Pick type C with a prevalence not of 60, but of 0.07 in 100,000; Tay-Sachs, 0.3 in 100,000.

This means, for instance, for Washington, DC with a population of 650,000 inhabitants, 5 patients with Niemann-Pick type C and just 2 with Tay-Sachs.

What about clinical trials in ultra rare diseases? Designing and performing a clinical trial in such diseases is very challenging for four reasons.

First, the small number of individuals that can be theoretically recruited.

Secondly, patients with these diseases are often severely impaired, are not able or willing to participate.

Most patients are children. For instance, a Niemann-Pick type C, 50 percent of the children die before the age of 13, which makes recruitment, of course, even more difficult.

Finally, the statistical design, which was already mentioned by my colleague. The conventional use—the so-called sample size calculation with a sufficient statistical power—can only be theoretically implied in such diseases, but will not be useful if you have, for instance, only 16 patients in the U.S. suffering from a rare gangliosidosis.

Nevertheless, we have to perform clinical trials to get an approval in ultra rare diseases. From my point of view, there are three prerequisites which have to be fulfilled for such trials and which can be called the "Triple D's": disease, drug, and the design of the trial in particular in terms of outcome measures and statistical analysis.

Disease in terms of four aspects:

The prevalence should be really low, less in 1 in 100,000.

The precise diagnosis has to be made, nowadays by genetic testing.

The disease should have a high impact in terms of signs and symptoms, but also functioning and quality of life, not only of the patient, but also the caregivers.

There is a high medical need and no other treatment available yet.

When it comes to the drugs, there are also four aspects:

Ideally, a drug should already be approved for a different indication, but means repurposing of drugs.

It should have a very good safety profile.

The efficacy should be shown in animal studies without a placebo effect.

The mode of action should be known on every level. That means histopathology, electrophysiology, even up to proteomics.

Finally, the design of the study and the outcome measures, they should always be clinically meaningful in terms of functioning and quality of life.

Imagine a patient is now able to walk or use their hands properly, take the tablets, take the meals by him or herself as you will see in one of the videos. This is a major improvement.

What could be the impact of adjusting the approval measures for pharmaceutical companies and research? We live in a world of commerce, investment, making money also by pharmaceutical companies. This is important, not only for the shareholders, but also for patients.

How is this related to the topic? If the approval of drugs for ultra rare diseases is adapted to the real world and transparent for such diseases, I think these diseases will become commercially more attractive. Companies will invest money because they have a chance that the drug is going to be approved within a reasonable time.

What is my personal vision? We live in the century of personalized medicine, and this attitude, I think, should also be transferred to rare diseases so that we have an individualized and harmonized

approval process for therapies based on solid science and the safety of drugs.

Finally, as a passionate doctor seeing 2,000 patients per year, a final statement; one should not withhold effective drugs from currently severely affected individuals because of regulatory approval processes, which may no longer be justified.

I am going to show, we have several examples. One patient with Niemann-Pick type C, we have published a case series, which is our approach to find new drugs on 13 patients.

[Video Presentation.]

Dr. STRUPP. Here you see a 14-year-old girl, who should perform the so-called 9-hole peg test, which is a standard test to evaluate hand coordination.

In a few moments, you will see what happens if this girl is on medication. This is just a simple case and that is our approach.

We use a drug which has been approved for other indications, which is definitely safe, and then we start with small case series. Knowing the mode of action of the drug, this drug normalized membrane potential.

We complement that by back translational research with this drug with the Department of Pharmacology in Oxford in appropriate animal models showing the same effects with this drug in the dosages which are per kilogram identical to the patients.

Chairman PAUL. This is approved where?

Dr. STRUPP. What?

Chairman PAUL. This drug is approved where?

Dr. STRUPP. This drug was approved since 1957 in France to treat patients with vertigo and dizziness.

My background is electrophysiology. I know the mode of action. It normalizes membrane potential and therefore I thought it may have an impact on various neurological disorders to bring neurons, which are still alive, but which are not working properly, into a normal state, and this we have seen for Tay-Sachs disease.

Chairman PAUL. Do you know how long the application process has been going on in the United States for this drug?

Dr. STRUPP. We had on July 17 an F.D.A. meeting. That was our first meeting with the F.D.A. We were able to introduce two new outcome measures for our trials, and the F.D.A. was quite positive that we can run a Phase II trial in the U.S.

We have also got an approval by the European agencies in U.K., Spain, and the Netherlands, which were quite enthusiastic, in particular since this drug has an excellent safety profile. It is well-tolerated.

By the way, hundreds of patients take the drug, now worldwide, off label, of course, from the Philippines, India, to Latin America and also in the U.S.

[The prepared statement of Dr. Strupp follows:]

PREPARED STATEMENT OF MICHAEL STRUPP

1. Chairman Paul, Ranking Member Casey and Distinguished Members of the Subcommittee, my name is Dr Michael Strupp, a Professor of Neurology at the University of Munich, Germany in the Department of Neurology and German Centre for Vertigo and Balance Disorders.

2. Thank you for the opportunity to discuss the current status of orphan drug development, and how the process of getting new treatments to patients with rare,

fatal, genetic conditions can be improved so that patients have access to potentially life-changing treatments sooner, and the extremely high medical need of too many orphan disorders can be met.

3. My clinical expertise is concentrated on diagnosis and therapy for vestibular, ocular motor, and cerebellar disorders, namely by discovering, investigating, and the "repurposing" of drugs by initiating, designing, and performing randomized controlled clinical trials (mainly investigator initiated) that include multinational studies. This also involves performing back-translational research in animal models.

4. Some of my major achievements in discovering and assessing new treatments have been: First, demonstration of the effectiveness of vestibular exercises in acute vestibular neuritis in a controlled clinical trial. Second, demonstration of the benefit of steroids in acute vestibular neuritis, a placebo-controlled, four-arm trial published in the New England Journal of Medicine. Third, introduction of three new pharmacotherapeutic principles for the treatment of rare diseases: (1) aminopyridines, as potassium channel blockers, for the treatment of downbeat, upbeat and central positioning nystagmus as well as episodic ataxia type 2 (now the treatment of choice for episodic ataxia type 2 according to the American Academy of Neurology, 2018); (2) chlorzoxazone for the therapy of downbeat nystagmus; and, more recently, (3) N-acetyl-leucine for the treatment of ataxias (such as inherited cerebellar ataxias like Ataxia-Telangiectasia and Spinocerebellar Ataxias), Niemann-Pick Type C (NPC), Tay-Sachs disease, as well as additional rare lysosomal storage disorders and neurodegenerative diseases.

5. I have been the principal investigator of the following randomized controlled trials on: episodic ataxia type 2 (in collaboration with Dr Joanna Jen, UCLA), downbeat nystagmus (in collaboration with Dr Christopher Kennard, Oxford), Meniére's disease, vestibular neuritis, vestibular migraine, vestibular paroxysmia, benign paroxysmal positional vertigo and ataxias.

6. Since 2016, I have been the head of the task force for the pharmacotherapy of cerebellar disorders.

7. I have also extensive experience in managing patients with rare, neurodegenerative diseases, in particular, cerebellar ataxias, NPC (including the 2017 "Recommendations for the detection and diagnosis of NPC" with Dr Marc Patterson, Mayo Clinic) and Tay-Sachs disease. I have also carried out both experimental researches to identify potential therapies for these patients. The background for this basic and clinical research has been an international collaboration requiring colleagues and experts' involvement from around the world. Back-translational research has also been done in various animal models, e.g., in close collaboration with Professor of Pharmacology and Neurology from various global institutions.

8. I have authored 366 PubMed listed papers and four books on vertigo, dizziness, ocular motor and cerebellar disorders. Currently I am the Editor-in-Chief of Frontiers in Neurootology, Joint Chief Editor of The Journal of Neurology, and a Member of the Editorial Board of Neurology. I have received many clinical and scientific awards, including the Hallpike-Nylen Award 2106, am a very engaged teacher and was awarded 'Best Teacher' by the German Neurological Society.

9. Finally, I am a very passionate doctor, and personally see more than 2000 patients per year, and am a proud father of four kids.

10. My curriculum vitae is attached.

Problem Statement

11. The responsibility of any clinician is to provide their patients with the best standard of care to manage their underlying conditions. Diagnosis is the traditional basis for decisionmaking in clinical practice and can provide crucial information on treatment options that influence outcome. Clinical management of rare, genetic, orphan diseases—a majority of which are progressive, debilitating, and display a large degree of clinical heterogeneity—follows a similar clinical practice paradigm to precisely diagnose the disorder, for instance, by genetic testing. In other words, delivering the best standard of care ideally requires clinicians do not simply treat symptoms of unknown etiology but identify the disease with a known underlying pathophysiological mechanism to apply a specific individualized therapy.

12. In my professional experience spanning 20 years as a neurologist, I have continuously diagnosed and treated patients with various different rare, genetic diseases. Such diseases often manifest in early childhood and are often associated with a decreased life-expectancy. Almost all of these diseases are associated with a severe impairment of functioning and quality of life. There is therefore a need to recognize

the significant disease burdens on both the patient as well as their families and caregivers.

13. For a majority of rare diseases, there are currently very few, if any, effective treatment options. For over 95 percent of orphan diseases, there is no US Food and Drug Administration (FDA) approved treatment medically available to help treat their condition. [1]

14. As part of my clinical practice, I have been fully committed throughout my career to identifying novel pharmacotherapeutics which could positively impact the quality of life of my patients and improve their standard of care. Throughout my research efforts, I have discovered three new potential therapeutic options (use of aminopyridines, Acetyl-Leucine and chlorzoxazone) for the treatment of rare diseases based on a therapeutic rationale to justify further clinical development. Specifically: the pharmacological agent should be approved for other indications so that it can be "repurposed" for therapeutic use in a rare disease setting; there should be available evidence in other disease settings to establish an acceptable safety profile in humans; there should be sound scientific evidence from animal studies elucidating the compounds mode of action and specific effects in particular diseases to establish the therapeutic potential of the re-purposed agent to treat a rare disease.

15. In my 20 years' experience in treating rare, often fatal, genetic disease, I have become acutely aware of the barriers which often limit potentially life-changing treatments from becoming available for rare disease patient communities. My personal perspective has also been shaped by my own experience as the initiator and principal investigator of seven "investigator initiated trials" (IITs), as well as my interactions and relationships with my rare disease patients and their families.

16. These experiences and interactions have helped me to identify specific considerations that are of practical relevance to research and development of new treatments for orphan diseases. From this basis, I believe the following issues ought to be considered and resolved in order to facilitate research and development of new treatments for orphan diseases.

New "Gold Standard" for Rare Disease Trial Design

17. In a progressive, life-threatening condition, there is a greater immediacy for trials to be carried out and in a maximally efficient manner so that the new treatment can be made available before the possible window of therapeutic opportunity is lost. There is an urgency from patients with rare, fatal diseases to have access to potentially life-changing treatments before they are too far progressed, or pass-away due to an absence of therapies.

18. Patients with rare, fatal diseases would benefit if regulatory authorities could collaborate more closely to design non-clinical programs, clinical trials, and endpoint assessments that are relevant to what is known both about the product-specific nature of the active pharmacological substance, and the patient population it intends to treat.

19. For example, non-clinical safety pharmacology studies in animals that assess the reproductive and developmental toxicity, carcinogenicity, and fertility and early embryonic development for diseases that predominately affect pediatric patients and are highly debilitating, rapidly progressive, and fatal, could be agreed to be conducted post-approval, or waived in exceptional circumstances on a case-by-case basis taking account of the severity of the disease and the patient characteristics.

20. The current conventional "gold standard" for a randomized, controlled trial (RCT) that shows statistical significance of $p < 0.05$ is often not an appropriate approach for a trial designed for rare, fatal, orphan diseases that progress rapidly and have high clinical heterogeneity. While RCT are desirable to establish clinical efficacy against a very high regulatory standard, their practical implementation can be challenging in a rare disease setting. Moreover, there are important medical and ethical concerns about certain RCT against a placebo to establish the therapeutic effects of the new treatment that may inhibit the rate of patient enrollment.

21. Parents and caregivers often have legitimate ethical concerns about placebo-controlled trials. This makes recruitment a long, difficult and complicated process, delaying the time it takes to get treatments to patients. It also greatly increases the costs of studies as multinational centers are needed to recruit a likely even smaller pool of willing patients.

22. This risk is even greater for trials involving drugs that are already approved for use in another clinical setting, i.e. "repurposed drugs" and could be readily

[1] *https://globalgenes.org/rare-diseases-facts-statistics/*.

accessed by patients for use in an off-label/unlicensed setting. In such circumstances, patients or their families may be reluctant to participate in a placebo-controlled study where there is a 50 percent chance that the trial participants receive an inactive treatment.

23. The standard approach to statistical significance is a prerequisite for large trials in diseases with a high incidence or prevalence, but for orphan populations this is hard to achieve in view of the rarity of occurrence of the disease and limited number of patients who are eligible for enrollment.

24. Many rare diseases are at a dual disadvantage due to the small sample sizes and the combination of high inter-individual variability in clinical course of the disease. This significantly diminishes a study's statistical power to detect a therapeutic effect.

25. In too many instances, when a compound fails, it is not clear if this is due to a lack of a biological effect rather than a failure due to an inadequate study design that was not compatible with what can be reasonably asked of, and measured within the rare disease patient population. Early collaboration with the regulators allows for alternative trial designs, in particular clinically relevant end-points, and statistical techniques that maximize data from a small and heterozygous patient population and increase ability to demonstrate effects of a treatment.

26. In rare diseases, a more balanced approach using smaller sample sizes and a wider array of assessments may be justified to establish the true clinical effects and patient-oriented benefits of the new treatment.

27. Clinical programs should be designed to consider the realities of the demographics of the patient population and their unique medical need should be the "gold standard" for developing orphan drugs so that they get to patients sooner.

Assessing Clinical Meaningful Effects

28. To get treatments more speedily to patients, the therapeutic effects should be established by reference to a wider range of data, including animal models, compassionate use data and patient/family self-reporting should be used to assess the efficacy and risk-benefit of a treatment. Such a holistic approach to evidence generation will serve our patients better, particularly in view of a clear unmet need for new treatments, and provide our patients with the optimal care that treating physicians strive to achieve as the clinical objective.

29. In orphan diseases that are rapidly progressive and display a wide range of debilitating symptoms, the best measurement clinicians have to determine whether a treatment improves patients' functioning and quality of life is to actually listen to the voices of patients and their families/caregivers' voices.

30. In patient populations with a huge variability of clinical symptoms, medications often produce different benefits in different patients, and it is not responsible to select a single measurement that is described as "clinically meaningful" for every patient success of the trial hinges upon.

31. In addition, quantifiable endpoints like biomarkers or symptom-rating scales may in fact be irrelevant for a patient's quality of life, level of functioning, or capabilities.

32. Therefore, in orphan disease trials, a wider use of clinical outcomes, including clinical impressions from neurologists experienced in treating rare conditions and familiar with the patient's individual disease presentation, as well as patient/family/caregiver reported outcomes should be the standard of success, and prioritized over statistical significance on a single primary endpoint.

Conditional Approvals and Continued Safety Monitoring:

33. A greater use of conditional approvals should be applied by the regulatory authorities to get drugs sooner to patients with high unmet medical needs. If an acceptable risk-benefit profile of the drug is established, albeit based on a dataset that is less than perfect, in the circumstances of treating rare, fatal, rapidly progressive diseases, it should be made available for clinicians to treat their patients in a controlled setting without delay.

34. In cases of fatal conditions and small patient populations which makes trials more difficult, post-approval rolling monitoring of safety and efficacy in patient populations is preferable as it provides direct evidence on whether the drug is used safely and effectively in a real-world clinical practice. Such evidence is far more relevant than data generated in an artificially designed clinical trial setting.

35. Similarly, individual, personalized assessment could be a more feasible way to assess the treatment effect in ultra-small patient populations. In this scenario, the expert clinician assess the patient's condition while on medication for a defined treatment period, as well as their condition after stopping the medication, to determine the individual's response and if the medication can be continued. This approach is contingent on the safety and tolerability of the drug, but allows patients with unmet medical needs access to potentially life-changing treatments faster.

36. Conditional approvals and individual assessments could be excellent ways to meet the extremely high unmet medical need of far too many rare diseases. These are also often preferable to long development programs because many of these rare conditions are fatal in the early phase of childhood and children do not survive to adulthood. As clinical presentation evolves, these young and small populations will face difficulties transitioning from pediatric to adolescent while waiting for new treatments, and often regress too much or die before effective treatments are available.

37. Use of conditional approvals, based on the considerations of the unique risk-benefit profile an orphan drug has for its target patient population, and even, an individual patient, will get treatments to patients who simply cannot wait for perfect study data to be generated in pursuit of a specific scientific endeavor.

38. In summary, the non-clinical and clinical development programs for rare diseases should be realistic and implementable so that the right level (while not perfect according to the "gold" standard commonly applied to new treatments for larger populations) of evidence is generated to make an informed assessment of whether the benefits outweigh the risks. For re-purposed substances, the risks of the pharmacological agents in humans would have been established and such experience is highly relevant in the overall benefit/risk assessment.

Case Studies: Acetyl-Leucine

39. An example of a novel drug I discovered that is a potential treatment for rare, genetic diseases is a modified amino acid ester that is orally delivered: N-Acetyl-Leucine (which can be formulated as the racemic compound N-Acetyl-DL-Leucine, or single enantiomers N-Acetyl-L-Leucine and N-Acetyl-D-Leucine). Based on the available evidence, N-Acetyl-L-Leucine is believed to be the optimal form. Given the high unmet medical need, N-Acetyl-L-Leucine is initially being developed by IntraBio Inc for the treatment of three rare, genetic diseases: Tay-Sachs diseases, NPC, and inherited cerebellar ataxias (such as Ataxia telangiectasia, spinocerebellar ataxias, and Ataxia with Oculomotor Apraxia) before it is investigated for the treatment of broader neurodegenerative conditions such as Alzheimer's.

40. N-Acetyl-DL-Leucine has been approved in France since 1957 for the treatment of vertigo. The drug has been used in 10's of millions of people and over 100's of millions of dosages, and has a very well-established safety profile.

41. Based on evidence that N-Acetyl-Leucine impacted vestibular symptoms, I hypothesized the compound could have effects on ataxia patients because of the close anatomical, physiological and pathophysiological interaction between the cerebellar and vestibular systems.

42. Due to its established safety profile in vertigo, and what is known about the active pharmaceutical substance, compassionate use studies in Europe began for a limited number of patients with rare lysosomal storage disorders and neurodegenerative diseases. The effects of N-Acetyl-Leucine have now been observed in 18 indications, including Niemann-Pick type C (NPC), Tay-Sachs disease, and inherited cerebellar ataxias, as well as Lewy Body Dementia and Parkinsonian syndromes. In these diseases, the compound has been observed to have an effect on improving various neurological symptoms, including ataxia, coordination, gait and cognition as well as "functioning", and quality of life.

43. Subsequent *in vitro* and *in vivo* animal studies in diseases models such as NPC and Tay-Sachs disease have demonstrated symptomatic and even neuroprotective effects of the compound in both diseases. The dosage per KG in the animal models was equivalent to the dose used in patients, further evidence for its potential safe and effective clinical benefit.

44. In total, the large body of research formed over the past 10 years, produced by myself and fellow neurologists and clinicians, as well as pharmacologists and chemists, is evidence that shows the compound is safe and offers a good risk-benefit profile for these rare, genetic diseases. This is supportive of 60 years of established safety data generated by the compounds approved use in acute vertigo in France.

45. However, despite what is known about the active pharmaceutical substance, and the nature of these rare, fatal, rapidly progressive diseases with no available treatments, the development of N-Acetyl-Leucine has been almost the same as drugs intended to treat broad, common, non-serious diseases.

46. As an example: the FDA requests a juvenile animal toxicity study (a year-long study) be conducted before N-Acetyl-Leucine is trialed in the US for pediatric patients (although they are over 50 percent of the patient population). Taking into account what has already been documented in another clinical setting regarding the active pharmaceutical substance, which provides reasonable confidence in the safety based on prior human exposure, this study does not complete the "knowledge gaps" and provide a greater understanding of pharmacological properties, but it does significantly delay clinical trials for patients with high unmet medical need.

47. Similarly, the clinical development of N-Acetyl-Leucine is still contingent upon demonstrating its success in randomized controlled trials with quantifiable data. However, from compassionate use experience, where quantifiable data demonstrating N-Acetyl-Leucine's statistical significance has been generated, we have also observed the significant value of assessing wide range of evidence, including reports from clinicians and families qualifying the compounds effect, to dozens of videos demonstrating the treatment effects. In a randomized controlled trial setting, these clinician and patient reported outcomes are still considered to be secondary and not relevant for regulatory approval, because they cannot be quantified and turned into traditional statistics. This has the potential of demonstrating a false-negative for the efficacy of a compound which could be indeed beneficial.

48. Evidently, the current regulatory requirements for every new proposed drug create barriers for getting potential treatments to patients with huge medical needs. Although it is necessary to properly establish the good risk-benefit profile of any treatment, the longer this process, the higher the potential patients turn to dangerous alternatives, like unlicensed use or using chemical grade products, due to their extremely high unmet medical need.

Actions

49. As a clinician, it is my responsibility that patients receive products whose quality is suitable for clinical use. Especially for conditions that are fatal and debilitating, it is important these products are investigated under the supervision of a clinical expert or specialist to determine their true risk-benefit profile.

50. That treatments of clinical quality can be made available sooner for clinicians use to care for their patients with rare, fatal diseases, the necessity of demonstrating a good risk-benefit profile needs to be defined within the context of the rare patient population's unique, unmet medical needs. Regulators and orphan drug developers have to exercise a sense of proportion when designing development programs so that the development process is ethical, efficient, and achievable, and patients must always come first with the prerequisite that an agent has been shown to be safe.

51. Most importantly, to improve the lives of patients with rare, fatal, often rapidly progressive, debilitating genetic diseases, we must listen to the voices of patients, their families, and caregivers so that the clinical effects are put into a proper clinical context.

52. There is no better judge to determine if a treatment will improve a patient's functioning and quality of life than the patient, their families, or caregivers, because no one will know better than what life with such diseases entails than patients, their caregivers, and their families—even neurologists like myself (and as a father of four children).

Chairman PAUL. Thank you. Since I have already broken the rules, and I know Senator Casey has to leave, do you want to inject with a question now before you leave?

Senator CASEY. Maybe I will just wait for the testimony of the following group.

Chairman PAUL. That is fine.

Our next testimony will come from Lincoln Tsang, a partner at Arnold & Porter in London.

STATEMENT OF LINCOLN TSANG, F.R.PHARM.S., PARTNER, ARNOLD, PORTER, KAYE, SCHOLER, L.L.P., LONDON, ENGLAND, UK

Dr. TSANG. Mr. Chairman, Ranking Member, and distinguished Members of the Subcommittee.

My name is Lincoln Tsang. I am grateful for the opportunity to discuss certain technical and regulatory issues relevant to facilitating research and development approval of new treatments to ensure their timely access by patients with rare diseases.

My statement is drawn upon my experience as a medical scientist, a former regulator, and now a private legal practitioner.

We have heard the dispassionate and very powerful statements from the patient representative and two eminent clinicians with extensive experience in the care and management of patients with rare diseases, as well as expertise in clinical trials for innovative products in these disease settings.

I therefore will limit my statement to reinforce what they have already said, but will place great emphasis on the regulatory policy based on my experience and understanding of the regulatory landscape in the United States, as well as in the European Union.

There is a greater need now for new methods of diagnosis and treatment for rare diseases. Health care delivery is now increasingly focused on planning the patient journey to improve quality and efficiency of clinical management, and to alter the focus of care tools and the activities most valued by patients.

The regulatory landscape may need to reflect more accurately the advances in science and technology, and a changing treatment paradigm which is increasingly patient-focused.

Many developed countries have introduced, at different times, orphan legislation to incentivize development of orphan drugs. Contrary to general belief, being designated as an orphan drug does not automatically allow a regulatory authority to approve it more quickly or with less evidence than drugs intended for non-orphan populations. The standard for a product approval is still based on satisfying the criteria for safety, quality, and efficacy.

Given their statutory role as guardians of public health and patient safety, regulatory authorities understandably require a robust and comprehensive dataset to be provided to reduce scientific uncertainty.

Clinical development to prove safety and efficacy of a new product is most costly. It is also most challenging for new therapies intended to treat orphan diseases given the limited pool of patients that the clinicians have alluded to earlier on.

The problem from a resource perspective is the need to set up multiple trials to meet different regulations and requirements. The solution would be a common trial design, but this may not be possible; although, international authorities may establish so-called parallel scientific advice, such as between the European Medicines Agency and the Food and Drug Administration. The respective agencies do not have to arrive at the same view on the study design.

The standard for approval of orphan drugs is legally the same as the standard for approval of all other drugs in the United States, as I understand it. The F.D.A. requires substantial evidence of ef-

fectiveness derived from adequate and well-controlled investigations.

The F.D.A. has the authority to apply the regulations flexibly, and has done so in many cases, but there is no obligation for the agency to do so.

In Europe, it adopts essentially the same regulatory standard. However, it is recognized by the E.U. legislature that in certain exceptional circumstances, a product license may be granted on the basis of less comprehensive data. In addition, for certain rare, life threatening, and debilitating conditions, the E.U. legislature has created a regulatory pathway for a temporary license, so-called conditional approval, to be granted subject to annual renewal based on reassessment of the benefit risk assessment.

The temporary conditional approval accepts that there is uncertainty of the submitted data, but recognizes also the immediate access to the product in view of an unmet medical need is sufficient to justify its approval. The uncertainty of the scientific dataset will be addressed post-approval to generate more comprehensive data.

A delegated regulation has been adopted by the European Commission to give greater clarity of the situation in which post-approval of efficacy may be required. The legislative directions encourage greater use of alternative clinical trial design and post-approval real world evidence.

It is my understanding the U.S. Congress has the legislative power to provide clearer directions to the F.D.A. to fully embrace less conventional and/or less commonly seen methodological approaches to establish clinical safety and efficacy in exceptional circumstances so that a new therapy is not unjustifiably denied or delayed.

True regulatory risks and scientific uncertainties can be managed through specific enforceable post-approval safeguards or commitments to monitor safety and efficacy. This flexible and pragmatic approach may serve the public health imperative of improving patient care in a setting where there is a demonstrable unmet medical need.

It has been said in various published literature that when a treatment method fails, researchers must be clear that there is a true lack of biological effect, rather than failure due to inadequate study design. Therefore, the approval process ought to take full account of the detailed knowledge of the broader sources of information to help determine what is the right level of evidence to support safety and efficacy of a new therapy.

In this context, Mr. Chairman and Senators, consideration should be given to the following points:

First, what constitutes an adequate level of scientific evidence to presume strongly a favorable benefit-risk balance to support product approval?

Secondly, is it feasible or practical to generate comprehensive data within a reasonable timeframe following approval?

Thirdly, can the scientific uncertainty of the submitted dataset be resolved by specific and enforceable post-authorization studies, including real world evidence?

Clinical development, as my colleagues on my right have already said repeatedly, clinical development is increasingly globalized.

Greater cooperation amongst various national and regional regulatory authorities to agree on a design of multiple center clinical trials will greatly facilitate the efficient execution of product development in this particular rare disease to serve the patients with rare diseases and to optimize their care and management.

We can strive to obtain the perfect dataset, but the patients cannot wait. It is possible with international cooperation to rely upon one well designed clinical study to elucidate the true treatment effects of a transformative method of treatment.

Mr. Chairman, Senators, I thank you again for your attention, and I am very happy to take any questions.

[The prepared statement of Dr. Tsang follows:]

PREPARED STATEMENT OF LINCOLN TSANG

Mr Chairman, Ranking Member and Distinguished Members of the Subcommittee, my name is Lincoln Tsang.

Thank you for the opportunity to discuss certain technical and regulatory issues that are viewed as relevant to facilitating research development and approval of new methods of treatment to ensure their timely access by patients with rare diseases. My statement is drawn upon my experience as a medical research scientist, a regulator and now a private legal practitioner.

I am a partner in the international law firm of Arnold & Porter. I am based in its London office. My practice is focused on regulatory, compliance, enforcement, market access and public policy concerning the life sciences sector. Much of my practice involves cross-border related matters. Prior to joining the law firm in November 2002, I was a senior official of the UK regulatory agency, the Medicines and Healthcare products Regulatory Agency (formerly the Medicines Control Agency) where I worked for nearly 13 years and latterly as its head of biologicals and biotechnology. During my tenure in the UK regulatory agency, I served as the UK representative on various advisory committees within the European Medicines Agency, and as an advisor to the European Commission, the Council of Europe, and the World Health Organisation. I also liaised on behalf of the UK regulatory agency with other regulatory authorities including Food and Drug Administration (FDA) in the United States, HealthCanada, Australia Therapeutic Goods Administration on certain matters of common interest. I was previously appointed by the European Commission to represent the European Union on the International Conference on Harmonisation on the technical requirements for pharmaceuticals, an international cooperative effort which was initially founded by the United States, the European Union and Japan. This cooperative initiative has been expanded considerably in terms of its geographical reach and the adopted regulatory technical guidelines are accepted world-wide.

I have also been appointed by UK Ministers to serve on various advisory committees in such capacity as a non-executive director of the National Institute for Biological Standards and Control, a Commissioner of the British Pharmacopoeia Commission where I have served as Chair of its Subcommittee on Biologicals and Biotechnology and Vice Chair of its Subcommittee on Nomenclature, and a non-executive member of the Regulatory Oversight Committee of the Health Protection Agency. Most recently, I was appointed by the Council of Europe to serve as its special advisor to assist in developing its Convention on combatting counterfeit medical products.

Before I joined the UK government services, I was a medical research scientist of a research team funded by Cancer Research Campaign (now Cancer Research UK) that involved in the development of anti-cancer drugs, one of which has now been approved for clinical use worldwide for treating brain tumours, namely glioblastoma in adults, and gliomas in children and adults. I started my career working in the National Health Service in the UK.

I have lectured on life sciences regulatory law and public policy at various universities including Yale University, University College London, King's College London.

My brief curriculum vitae is attached.

Challenges in Developing New Treatments for Rare Diseases

Innovative medical technologies and medicines are critical to improving health and well-being.

Medical advances in science and technology, including genomics, will open up avenues to develop new therapeutic approaches in advanced therapies based on gene, cell and tissue engineering, and to re-purpose already approved drugs for new therapeutic indications with a view to addressing diseases and conditions where there is an unmet medical need.

However, the potential for these new therapeutic approaches can only be realised if they are approved for clinical application to optimise care and management of patients.

Healthcare delivery is now increasingly focused on planning the patient journey, to improve the quality or efficiency of clinical management and to alter the focus of care toward the activities most valued by the patient. There is a greater need now for new methods of diagnosis and treatment for rare diseases. There may be as many as 7,000 rare (commonly known as "orphan") diseases, [1] many of which are life-threatening or debilitating, where there exists no authorised or satisfactory method of treatment. They affect most critically the very young who often do not survive beyond adolescence. Without treatment, their quality of life will be seriously affected and their lives may be shortened. This represents the grim reality that many of these patients and their families are facing.

Orphan legislation varies amongst the developed countries and was introduced at different times. The United States led the way by enacting the Orphan Drug Act of 1983 which introduced an incentive system for the development of orphan products in the US. Following the introduction of the US Orphan Drug Act, a number of developed countries and regions built a regulatory framework designed to provide incentives for companies to develop products for orphan diseases, which would not normally justify investment in research development or marketing, owing to their poor financial return. Apart from the EU, countries such as Japan, Australia and Singapore have developed their own regulatory frameworks to encourage the development of products for orphan diseases.

The clinical development of new technologies intended to treat rare diseases is fraught with practical challenges. There may be disease-specific complexities, such as poor understanding of the natural history of the therapeutic indication due to there being little information available about disease progression, variable phenotypic characteristics of the patient populations and clinical courses, geographical dispersion of a small number of patients and the relative paucity of published clinical trials to inform study execution.

In order to establish the clinical efficacy and safety of new methods of treatment, the randomised controlled trial has been accepted by regulatory authorities around the world as the gold standard. This trial design minimises selection bias in order to elicit the true treatment effect of the new therapy.

Whilst this classic study design is commonly used in studies of new therapies designed to treat common diseases as it may involve a large number of more readily available clinical trial subjects, this may not be feasible in a small population. By necessity, clinical trials in rare diseases enrol fewer trial subjects who may not necessarily be concentrated in a particular geographical region. In combination with significant clinical differences between trial subjects (commonly known as inter-subject variability) observed in many rare diseases, this diminishes the 'power' of the study to detect a therapeutic difference. Statistical power is the likelihood that a study will detect an effect when there is an effect there to be detected.

Given the rarity of orphan diseases, the timely and adequate recruitment of eligible trial participants is recognised as a challenge to initiate and complete a study. For new treatments intended for a larger patient population, regulatory authorities may often demand two or more pivotal confirmatory studies sufficiently powered to be carried out, and this may necessarily involve a relatively large patient population. As has been recognised by the US and EU regulatory authorities, such a re-

[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. In the EU, an orphan condition is defined as a life-threatening or debilitating disease or condition affects less than 5 in 10,000 persons in the EU. In Japan, a disease or condition is considered rare if it affects fewer than 50,000 patients or less than 40 in 100,000 based on the population in Japan.

quirement is more challenging to satisfy for treatments intended for orphan conditions.

Because of the low incidence of the disease in each country given its rarity, there is often a need to enrol patients from a number of countries to obtain a large enough sample size of trial subjects to establish the clinical efficacy. Since trial subjects are geographically dispersed, multi-centre studies must be initiated in various international centres of excellence. Technically speaking, the problem (from a resource perspective) is the need to set up multiple trials to meet different regulations and requirements. The solution would be a common trial design but this may not be possible, given varying regulatory approaches. The demand to satisfy various regulatory requirements is obviously more critical for small and medium sized enterprises with very limited resources.

Whilst certain authorities have established parallel scientific advice, such as FDA and EMA, the respective agencies do not have to arrive at the same view on the study design, such as the parameter(s) used to measure the clinical outcome following administration with the new therapy (commonly known as an endpoint or variable). This may become a practical issue in the final analysis of the data derived from studies with disparate trial designs.

In a rare disease setting, there is clearly a tension between the need for transformative innovation to treat such devastating conditions which require a considerable time, financial investment in research and development, and the need for timely patient access to such innovation. Innovation will not serve the public health imperatives, and most importantly patients, if it is not approved, adopted and diffused in the healthcare system for the benefit of society at large.

In this highly regulated sector, the need for timely approval of innovative treatments to be accessed by patients with orphan conditions has attracted a great deal of debate and attention in recent years.

Approval of Treatments for Orphan Conditions

Given their statutory mandate as guardians of public health, regulatory authorities understandably require a dataset submitted for product approval to be sufficiently robust in the sense of its scientific certainty. On the other hand, patients and those involved in the care and management of such patients with rare, life-threatening and debilitating conditions, not unreasonably, expect expedited product approval to ensure timely access to such life-saving methods of treatment, whilst accepting the scientific uncertainty of the pre-approval dataset.

Regulatory authorities are mandated by their respective legislature to supervise product approval and post-approval processes to ensure that the marketed products are clinically safe and effective and of an acceptable quality standard. Timely access by patients to innovative methods of treatment in therapeutic areas with unmet medical need serves an important public health purpose, especially for those patient populations with a high disease burden, that represents the impact of a health problem as measured by financial cost, mortality, morbidity, or other health-related indicators.

In an evolving regulatory framework, striking the right balance of these competing interests relating to (a) regulatory control of innovation based on robust evidence and (b) timely patient access to transformative innovation, has been a continuing debate amongst the regulatory authorities, legislature, payers, healthcare professionals and most importantly the patients.

That said, although more flexibility could be introduced, regulatory authorities generally have the authority and some regulatory latitude to determine the level of evidence that is required to inform a benefit/risk assessment that underpins product approval.

Contrary to the general belief, being designated as an orphan product does not automatically permit a regulatory authority to approve it more quickly or with less evidence than drugs intended for non-orphan populations.

As a general matter, it is my understanding that the standard of approval for orphan product is legally the same as the standard of approval for all other drugs in the US. The FDA requires 'substantial evidence' of effectiveness derived from 'adequate and well controlled investigations'. Whilst FDA has the power to apply the

regulations flexibly,[2] and have often done so in the orphan drug context, it is under no obligation to do so.[3]

In the EU, the adopted regulatory standard for approval[4] is that clinical data should be based on 'controlled clinical trials' if possible, randomised and (as appropriate) versus placebo and versus an established medicinal product of proven therapeutic value. Any other design must be justified. The treatment of the control groups will vary from case to case and also will depend on ethical considerations and therapeutic area; thus it may, in some instances, be more pertinent to compare the efficacy of a new medicinal product with that of an established medicinal product of proven therapeutic value rather than with the effect of a placebo.

The EU legislature has recognised that in certain exceptional circumstances, a marketing authorisation may be granted on the basis of less comprehensive data[5] either where because the disease is rare that comprehensive clinical data cannot reasonably be generated under normal conditions of use, or where in the present state of scientific knowledge, comprehensive information cannot be provided, or where because it would be contrary to generally accepted principles of medical ethics to collect such information it would not be possible for a manufacturer to provide comprehensive data. These are all circumstances in which it may be justified to grant a marketing authorisation in order to address an unmet medical need under exceptional circumstances to advance patient interests.

In addition, for certain rare, life-threatening and debilitating conditions, the EU legislature has created a regulatory pathway for a conditional marketing authorisation to be granted, subject to annual renewal, based on a re-assessment of the benefit/risk.[6] The grant of such an essentially "temporary" marketing authorisation is based on certain specific conditions being satisfied. Whilst accepting that there is uncertainty as to whether the submitted clinical data can comprehensively elucidate the benefit/risk balance of a medicinal product, the immediate access to the product in view of an unmet medical need is sufficient to justify its authorisation, provided that the manufacturer is able to provide the comprehensive data post-authorisation to confirm the benefit/risk balance.

A specific Delegated Regulation has been adopted by the European Commission in order to provide the EMA and the EU national regulatory authorities with greater clarity of the situations in which post-authorisation efficacy may be required, such as (a) where concerns relating to some aspects of efficacy of the product are identified and can be resolved only after the product has been marketed; (b) where the understanding of the disease, the clinical methodology or the use of the product under real-life conditions indicate that previous efficacy evaluations might have to be revised significantly.

The requirement for post-authorisation efficacy studies may arise, for example: if the initial efficacy assessment is based on surrogate (i.e. not clinical) endpoints which requires verification of the impact of the intervention on clinical outcome or disease progression or confirmation of previous efficacy assumptions; or uncertainties with respect to the efficacy of a product in certain sub-populations that could not be resolved prior to marketing authorisation and require further clinical evidence.

Regulatory Latitude

Many established regulatory authorities including the FDA in the US and EMA in the EU have declared in their respective mission statements that in addition to their role to safeguard public health and patient safety, they are responsible for ad-

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[2] While the statutory standards apply to all drugs, the many kinds of drugs that are subject to the statutory standards and the wide range of uses for those drugs demand flexibility in applying the standards. Thus FDA is required to exercise its scientific judgment to determine the kind and quantity of data and information an applicant is required to provide for a particular drug to meet the statutory standards. FDA makes its views on drug products and classes of drugs available through guidance documents, recommendations, and other statements of policy. (Code of Federal Rules Section 314.105).

[3] Saskinowski F. et al. Quantum of Effectiveness Evidence in FDA's Approval of Orphan Drugs DIA Therapeutic Innovation & Regulatory Science (2015) Volume: 49 issue: 5, page(s): 680–697.

[4] Part I Section 5.2.5.1 of Annex I to Directive 2001/83/EC.

[5] Part 3 Section 5 of Annex I to Directive 2001/83/EC.

[6] Article 14(7) of Regulation (EC) No 726/2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency; Commission Regulation (EC) No 507/2006 on the conditional marketing authorisation for medicinal products for human use falling within the scope of Regulation (EC) No 726/2004 of the European Parliament and of the Council.

vancing public health by helping to facilitate or otherwise expedite the approval of medical innovations to maintain and improve the health of patients.

In this case, it is my understanding that the US Congress has legislative power to provide clearer directions to FDA to fully embrace less conventional and/or less commonly seen methodological approaches to elucidate benefit/risk balance in exceptional circumstances so that a new method of treatment is not unjustifiably delayed or denied subject to certain specific post-authorisation safeguards to monitor the ongoing benefit/risk balance of the approved product.[7] Such an explicitly flexible and pragmatic approach may serve the public health imperative of improving patient care in a clinical setting where there is a demonstrable unmet medical need.

It has been said when a method of treatment fails, researchers must be clear that there is a true lack of biological effect, rather than failure due to inadequate study design.[8] Therefore, approval process ought to take full account of the detailed knowledge of the pathophysiology (meaning the disordered physiological processes associated with disease or injury) of the orphan disease and the pharmacology (meaning uses, effects, and modes of action) of the new method of treatment to facilitate the design of efficient clinical development which will in turn help determine the amount of clinical data required to inform an assessment of clinical efficacy and safety.

In the context of product approval in a rare disease setting where there is an unmet medical need, consideration should be given to the following points:

- What constitutes an adequate level of scientific evidence to presume strongly a favourable benefit/risk balance to support product approval?
- Is it feasible or practical to generate comprehensive data within a reasonable timeframe following product approval?
- Can the scientific uncertainty of the submitted dataset can only be resolved by specific and enforceable post-authorisation studies, including real-world evidence?

As indicated above, patients to be enrolled in clinical trials for rare disease are geographically dispersed and many clinical studies are conducted in various centres of excellence. Therefore, greater cooperation amongst various national and regional regulatory authorities to agree on the design of the multi-centre clinical trials will greatly facilitate the efficient execution of product development to serve the patients with rare diseases and to optimise their care and management. With strong international cooperation, it will often be possible to rely upon only one well-designed clinical study to elucidate the true treatment effects of a transformative method of treatment for all global regulatory authorities.

However, note also that even though the trial data demonstrate a favourable benefit/risk, in many countries, patient access may not be realised if the new therapies are not accepted on grounds relating to cost-effectiveness and affordability, given the increasingly cost conscious healthcare delivery systems.

Mr Chairman, Ranking Member and Members of the Subcommittee, thank you once again for the opportunity to provide this testimony. I am happy to answer any question.

Chairman PAUL. Thank you, Dr. Tsang.

Our last witness is Mallory Factor, who is a Professor at Oxford, and the Founder and CEO of IntraBio, Inc., which was founded for the purpose of developing novel therapies for rare diseases.

STATEMENT OF MALLORY FACTOR, FOUNDER AND CEO, INTRABIO, INC., OXFORD, ENGLAND, UK

Mr. FACTOR. Thank you, Senator Paul, and thank you also Senator Casey, for participating in this, as well as the other Senators.

My colleagues to my right, I think, have covered a great deal of material already. I am here today to share with you some observa-

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[7] This may be similar to the approach taken by the EU as explained above (see paragraphs 27–29).

[8] Dickson P.I. et al. Research challenges in central nervous system manifestations of inborn errors of metabolism. Mol Genet Metab (2011); 102: 325–338.

tions on some of the obstacles that delay, and even restrict, novel orphan therapies from getting to patients. And some of the ideas how orphan drug developers in the Food and Drug Administration, the F.D.A., could collaborate more closely to bring treatments for rare genetic diseases to the point of approval, so that they are available to patients with conditions or diseases for which there are high, unmet medical needs.

Rather than go over some of the same material that my colleagues have done, what I am going to do is I am going to give you a quick case study. A case study based on the actual compound you saw being used there.

IntraBio is a small biopharmaceutical company whose mission fundamentally is to advance patient interest and to develop novel therapies to treat fatal, rare, rapidly progressing genetic diseases with high, if not totally, unmet medical needs.

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 rare disorders like inherited Cerebellar Ataxias: Ataxia Telangiectasia, Spinocerebellar Ataxias, and Ataxia with Ocular motor Apraxia; Tay-Sachs disease, which there is another video, which I am sure can be distributed; Niemann-Pick disease Type C, which you just saw; as well as common neurodegenerative diseases like Lewi Body Dementia, a form of Alzheimer's; 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. Three in particular: Tay-Sachs, Niemann-Pick C, which you saw the video of, and inherited cerebellar ataxia subtypes. These predominately affect pediatric patients and are fatal, and they are rapidly progressive, and display a huge range of debilitating neurological as well as physical symptoms, and they have no treatments medically available.

IntraBio has commissioned further safety pharmacological studies to characterize the safety profile and further non-clinical studies to investigate the optimal form and the mode of administration for patients.

I have a lot of this material in here and rather than just read from it, I will talk to you extemporaneously.

Hundreds of millions of doses have been used of this drug since 1957; hundreds of millions. Tens of millions of people have been on this drug. Its safety profile has been shown to be safer than aspirin, and yet we cannot even begin to put it into people here yet in a trial.

I can go into great detail in the interactions with the F.D.A. The F.D.A. is first and foremost concerned with risk. What they need to be concerned with is risk benefit and timeliness. They do not understand the risk benefit analysis.

I am not sure what we can do, but the real problem is trying to reach somebody at the F.D.A. You cannot. It is impossible to sit down other than in a formal setting with months. It took us eight months to get a meeting, and I will not tell you how many children passed away from these diseases during those eight months, just to begin to have a discussion with them.

We submitted a 150-page briefing book, which I am not sure anybody really read thoroughly.

What we need is the ability to sit down with the F.D.A. And these are good people at the F.D.A., but we need to be able to sit down with them and have simple conversations.

There is a disease called GM1, which we have shown efficacy with our drug. We cannot do a trial because there are 16 people right now alive in the United States. You could not get statistical significance. What are we going to do? Nothing. We cannot. But we would love to be able to sit down and say, "How do we help these people?" since we are aware of these people using it unlicensed. Some of the people are even forced to buy chemical grade.

Our goal is very simplistic. We would like to work with the F.D.A. and the regulators to move forward on a timely manner and look at the risk benefit analysis. And that is what, I think, is vital.

The acts, the Orphan Drug Act and things like this are terrific, but they help after these trials. They do not get into the trials. They are after you get your N.D.A., your drug approval. That is where the benefit comes in. Not getting it to the people.

I thank you and again, the script will give you a lot more information than I have just given you.

[The prepared statement of Mr. Factor follows:]

PREPARED STATEMENT OF MALLORY FACTOR

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

[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.

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 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 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-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

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

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 (e.g. 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.

Chairman PAUL. Thank you, and thank you to the entire panel.

I would like to recognize Senator Casey for any questions.

Senator CASEY. I will be very brief.

You were all so compelling and your testimony was so captivating that I stayed longer than I had planned, and I am grateful that I did that, and grateful that you are here.

I will submit written questions because they are written with the aid of capable staff; they will be much more articulate than I could muster today, but we are grateful for the work.

Each one of you presented, I think, a challenge to us on these issues and we are grateful you took the time to be here and to provide your experience, your scholarship, and your passion. We heard that throughout the testimony.

Thanks very much.

Chairman PAUL. Senator Casey, thank you.

Hopefully, maybe we could talk some more about any updates to the Orphan Drug Act. We have heard some things maybe from Europe and other places that are working better.

Maybe you and I could work together and see if there is something we could do to streamline, to even do a better job. It sounds like there have been some benefits, but maybe there is something else we could do.

Senator CASEY. It is on the record. Yes.

Chairman PAUL. All right. Thank you.

I think we have had a good discussion. I want to go into it just a little more, and then also encourage everyone on the panel and everyone who is interested in this—I know Mr. Dant and your group, and other groups like yours that exist—to come together. Let us try to have an organization that brings together these suggestions for how we would update the Orphan Drug Act.

It sounds like, though, there was some success. Senator Casey mentioned that there were 15 drugs approved before the Act, and then all of sudden there are 600. But I think science is developing so rapidly—and we mentioned DNA sequencing and the individuality of treatment—that there may be a disease that only one person in the world has. You cannot really have a double blind clinical study for one person. You cannot have it for 15 people.

One of my questions, this might be for the scientists, is the idea that you have to have a double blind, randomly controlled study. Is that stopping a lot of what goes on with the Orphan Disease Act? Or does the Orphan Disease Act actually understand and already make some accommodations for the fact that the numbers are not big enough?

We will start with Dr. Strupp.

Dr. STRUPP. I totally agree. This is a very big issue. Personally, I have designed eight investigator-initiated trials, and very much moved in the design and also the statistical analysis. The key number is that you do a sample size calculation.

Doing a proper sample size calculation requires that you first have to estimate was this a clinically meaningful difference? So that is one of the parameters.

Then you have to add the power of the study and the alpha value, and then you often end up with sample sizes of 50, or 100, or 200 patients.

Chairman PAUL. That is then being accepted by the F.D.A. with the understanding that you cannot do 1,000 people?

Dr. STRUPP. Of course.

Chairman PAUL. Okay.

Dr. STRUPP. Two hundred would be accepted, but if you only have 50 in the U.S., you cannot do a proper statistical design and analysis in the conventional way.

Marc Patterson pointed out in his statement what are the potential alternatives for such analyses based on up to date, sophisticated statistics.

Chairman PAUL. But given the current situation, and you are saying currently it is not working, it is difficult to get the F.D.A. to approve studies for orphan diseases. Yes?

Dr. STRUPP. Yes.

Chairman PAUL. Dr. Patterson.

Dr. PATTERSON. Senator, thank you.

Just to come back to your point, the Orphan Drug Act, as you know, initially really incentivized companies to do studies, but it did not direct the F.D.A. as to how these studies should be conducted in rare diseases.

Chairman PAUL. Right.

Dr. PATTERSON. The Cure America Act, I think, was terrific. It was very encouraging in terms of asking the F.D.A. to explore adaptive trials, for example, and Bayesian approaches. But it did not say, "You shall do this."

I think that would be very important to give regulators those tools to say, "You have explored this. You have shown it is appropriate." There is quite a literature that shows that these trial designs may be effective.

Chairman PAUL. Right. We have had some of this debate in the past, like on using European studies or Asian studies. We had words put into the bill that said, "The F.D.A. shall do it," actually or, "must do it." Everybody said, "No, no. We can say that, 'They can.' "

The people softened the words because they said, "We do not want to tell the F.D.A. how to do their job." But at the same time, maybe sometimes we need to be more directive in the language because I think given the choice, often the status quo persists.

Dr. PATTERSON. Senator, I would agree with you completely. Thank you.

Mr. DENT. Senator, I would also add that patients across the Nation are jumping as fast as they can to get into the line to enter a trial.

The negative is the trial designs are sometimes so narrow that many do not qualify because the clinical endpoints are so very precise, even drugs during trial that seem to help. And the parents will tell you, "Yes, my child was speaking afterwards, and now they are not." And yet, the trial fails.

Trial designs of all-comer trials where, because of the heterogeneity of the disease, three siblings can sit next to each other, but they present completely differently. The drug may help one, but not the other two. We should look at all comers.

Trial designs like the Multi-Domain Responder Index, which really takes all comers, looks how they can succeed.

Chairman PAUL. I think that might be something that you could help us with particularly those who design trials. We talked about trial design being one of the things.

We have random, double blind studies as this gold standard that has been out there, and we have 1,000 people, it has to be, and it has to be half get it, half do not get it. That is not appropriate for terminal illnesses, small illnesses.

But if you could help us not just today, but as we go through this process, if we were going to talk to the F.D.A. or legislate how these are designed, because it still has to have some latitude as to how the designs are. But maybe we have a standard now for a design and maybe you can help us with defining what the new design would be to allow the process to work better.

Dr. Strupp.

Dr. STRUPP. May I add to that?

You saw this girl and if you just measure the time, that may be misleading because if coordination improves, they will often take longer time because they do it more precisely.

Based on that observation, the F.D.A. was very open minded when we suggested a so-called Clinical Global Impressions of Change. That means experts evaluate the changes having a look at videos. They are blinded; on-off, on-off the drug.

Chairman PAUL. I think even a layperson might be able to discover that drug seems to be helping.

But the only thing I would say is the only thing you would have to do to convince me is that it is not random. So you would have to have enough videos to show me that this little girl is not better some days and worse some days without drugs.

If there is no random improvement like that and you have that dramatic improvement, it should not take us 10 minutes to figure out that there is a great deal of benefit there.

Dr. STRUPP. Right. And then you do not need 50 patients. If I present you someone——

Chairman PAUL. Exactly.

Dr. STRUPP ——who is fluent in Spanish, it does not help to speak additionally Chinese.

Chairman PAUL. Right.

Dr. STRUPP. That is very convincing.

Chairman PAUL. Was this also the drug that has been treated for decades in France and so it is not something that is poison? It is not something that people are dying from. There are no safety problems.

Dr. STRUPP. You mention a very, very important point, and we always have very vivid discussion with the F.D.A. in terms of teratogenicity and carcinogenicity.

Imagine most of these diseases affect children. So teratogeneity is unfortunately not an issue because they will not have children. So why do we have to do animal studies in two animal models if we treat children at the age of 13? The same is true for carcinogeneity. If you have a life threatening disease with a significantly reduced life expectancy——

Chairman PAUL. It looks like you need a way to be able to short step this; that is able to look at this. Maybe like what Dr. Tsang

was saying in Europe, that you give a temporary approval much quicker.

What you need is something that a CEO in a company will do, but the government is very, very hard to develop things that are adaptable. The government is very, very rigid.

I know the F.D.A. wants the best. They do not want a horrible occurrence like we had with some of the things that were approved too quickly. But at the same time, I think, we are maybe, the pendulum is over here, and it needs to come back toward the middle.

You need to give someone the prerogative to actually look at a video like this and say, "My goodness, though. There are 16 people with this disease. Why do we not start more aggressively getting this to the people?" and still continue to study it. Maybe have a temporary, and have a review each year for safety.

We need to do something. I do not think we are doing enough.

Dr. STRUPP. I think we would even have a more impressive video with Tay-Sachs. I do not know if you have it in the files.

Chairman PAUL. We can show it if someone can find it.

Let us go to Professor Factor.

If someone wants to cue up, whoever is in charge of the video, if they can find the Tay-Sachs, we will look at that.

Mr. FACTOR. The key, really, from our perspective is early and frequent interactions with the F.D.A. to make the development programs, before the program begins even, before you do your filings that you have a working relationship with the F.D.A.

What the F.D.A. has to recognize more than anything else is the endpoint should be quality of life. And the patient and caregivers really know those endpoints better than anybody else. Quality of life should be the key.

They really need to have a separate track for fatal orphan drugs with high unmet medical needs. There has to be a separate track, which they do not have.

Chairman PAUL. Right.

Mr. FACTOR. I can give you—at some point I hope I have the opportunity—an example of how it took us eight months just to get a meeting.

Chairman PAUL. Well, I think all of those things are important. What we need to do is just take them and turn this into something constructive, and take the problems we are having, and let us look at the law specifically and see how we can change the law.

Like I say, some of this, we need the input of scientists on how to look at the parameters of what the government is saying we need for design to say, "How can we adapt that?"

I think it is a point well taken that the Orphan Disease Act was mostly about encouraging companies to invest in this, but it did not necessarily make the F.D.A. process easier.

Dr. Tsang.

Dr. TSANG. Thank you, Chairman.

I think that my colleagues what they have been saying is that the requirements must be applied in a proper clinical context. That is the key test so that we are not applying the requirements disproportionately.

Very often, it is very convenient for, as a former regulator, very convenient for regulators to say that, "I need to check all the boxes

and do it mechanically." But very often, the law actually provides——

My understanding of the U.S. legislation is no different from other jurisdictions. There is flexibility. The question here is whether or not regulators are prepared to exercise flexibility to be a bit more bold applying the requirements proportionately. That is a key test.

Chairman PAUL. Mr. Dant.

Mr. DANT. Thank you. I would add one thing, jumping on that as well.

There is great science already available that goes to what is referred to often as "the valley of death" where, because it takes so long to move great science through the pipeline to the F.D.A. and then to treatment, it costs too much. So companies cannot invest in science to move it along and so the therapies do not come forward.

That is the value of the Open Act, and the value of repurposing drugs, and how we can get those companies to jump into safe drugs that already are proven safe that may help treat.

Chairman PAUL. See, this has been the problem that I have been carping on for a while.

There is idiopathic pulmonary fibrosis. My political director's sister has it and the drug she uses, fortunately she lived in New York City had a family that had the wherewithal to get her into a trial. So having some means, you do not necessarily have to be rich, but you have to have the means to get to a center and then a family that was able to get her into a trial, but the drug had been legal in Japan for a decade.

The problem I have is that we are so rigid. Let us say there is a blood pressure drug, maybe 15 million people are taking it. Fifteen million people in France have been taking a blood pressure drug for 15 years. We are going to start over with all of the safety trials? Instead of having a great deal that the preponderance of evidence is that we should really shortcut these things.

I think wanting to have zero tolerance, we do not want to approve drugs that either do not work or are unsafe. But I think we have too much rigidity and as Dr. Tsang was saying, maybe some of it is getting people who are more open minded to do that.

We will talk with the F.D.A. director as well, who is a medical doctor, and see if we can talk some about the human element of being less rigid. But also, I think something needs to be done to the Orphan Drug Act to actually maybe separate a category or have a separate pathway just dedicated for the orphan drugs. But it is not going to be just orphan drugs. There is going to be——

I think people's individual cancer is already being treated in an individual way. We have had testimony from people with ALS or Lou Gehrig's disease, about how there are different varieties of it, and you are going to discover, and have a treatment, probably, for one person or ten people that are a variety of that. So we just have to figure out how to get beyond that rigidity.

Are we able to watch another video? Do you want to introduce it, Dr. Strupp?

[Video Presentation]

Dr. STRUPP. This was before treatment. It is an eight year old patient with a genetically proven Tay-Sachs disease. So without treatment, he could hardly stand unaided.

Now click on the other one on the football field.

That was 7 weeks later.

Chairman PAUL. You are convinced that this is not random? There is not that kind of random?

Dr. STRUPP. He was off, on, and off. Colleagues who saw him could not believe how much he improved. He did not support our football team, but nevertheless, he improved very much.

Go to the next slide, please. Click on the animal on the left and the right.

These are the complementary studies we are doing. This is a nice thing. This animal gets the same drug and the same dosage per kilogram. You see the major difference. Again, if you will measure the time it takes until the animal reaches the bottom, the non-treated will be faster because it falls down. So we just have to have a global impression.

Chairman PAUL. These studies are being done in Germany?

Dr. STRUPP. No. This is done in collaboration with Oxford, Frances Platt from the Department of Pharmacology.

Chairman PAUL. But then my question is if you want to show these studies, what are the odds that the F.D.A. is going to look at these studies that you have already performed or make you do them over?

Dr. STRUPP. They liked the videos very much on July 17.

Chairman PAUL. But are they going to be an acceptable part of your presentation, do you think, to the F.D.A.?

Dr. STRUPP. Yes.

Chairman PAUL. Good.

Dr. Patterson.

Dr. PATTERSON. Senator, just to comment. You very astutely mentioned the importance of deciding whether a change is random or not.

I think this is a beautiful example of where you can use an N-of–1 trial design where you can blind, in fact, both the patient and the observer.

You can be reviewing a videotape, so they do not know if the patient is on the placebo or the control. You can do that with appropriate trial designs, multiple N-of–1, and get the information you need which, I think, is still scientific.

Chairman PAUL. Show the reproductivity. This is somewhat the difficulty.

Alzheimer's does go up and down, the cognitive studies are sometimes difficult to prove one or the other because people have really good days. If you have had a parent or a grandparent with this, they have a really good day and then have a bad.

Once you can eliminate the randomness out of this, though, it should not be that much more difficult. We should take into account the fact that the drug has been used for a long time in France by lots of people.

Mr. Dant.

Mr. DANT. Senator, I would also add that in rare disease, natural history studies simply are not there because the diseases are so

rare, which speaks to Dr. Patterson's point about the importance of patient owned registries.

Our partners in industry oftentimes have their own registries, but there are silos of information that are not shared.

Chairman PAUL. What goes into a registry?

Mr. DANT. What the parent, what the individual with the disorder sees, feels, does. They enter it themselves and it becomes a living document that can be reviewed by physicians, by scientists, and by industry.

We need the F.D.A. to also look at those registries and understand that there is value in patient-reported outcomes.

The power of the patient in moving studies forward cannot be understated.

Chairman PAUL. We are in the middle of a vote, so we are going to wrap up pretty quickly. We have been doing an open forum, and I like this. Sometimes you get more from asking people what they want to say than asking them a specific question.

I am going to open it one more time and we will see if anybody has something they would add to the hearing as we wind up here. I am going to have to ask a question if you do not come up with anything.

Professor Factor.

Mr. FACTOR. I will add something very quickly.

The particular drug that we are talking about that is used in France contains gluten and things like this in it. We are just trying to use the pure form, which causes all sorts of other problems by just taking the pure form, the active part of it. It is called a racemate in the active form and is only part of it.

But to get rid of the gluten and some of the other stuff that people react to, that adds a whole bunch of new tests, which makes no sense.

Chairman PAUL. What I would like to do, and we are going to wrap up here, because I have to go over to the Senate floor and vote, is that I want to thank you all for testifying, for coming and taking your time.

You do not get rich being a congressional witness. You are not paid. In fact, actually, many of you probably paid your own way here as well, and we really appreciate that because you believe in what you are doing.

I really want to get a result. Just hearing testimony, we can do that. If nothing happens, then I am disappointed. So if you have further remarks or anything that you would like to submit in writing, if there are other groups like yours, Mr. Dant, that would also like to submit something in writing, we will accept that as well.

Then, let us continue the collaboration to try to see if we can do an update of the Orphan Drug Act that either has a separate track, different design perhaps. It is still my belief that whether it is an orphan drug or any drug, we live in world——

Look, Dr. Strupp is from Germany, but we do not say we are not going to listen to him because he is German. We have great doctors in Asia. We have doctors all over the world and all of these studies. The world, the modern, civilized world is an enormous world of medicine and science now, and we are crazy to stop it at the border and say, "No, you have to Americanize all of the studies."

I think the scientific community already is very international. All the meetings are international. The studies are taken and written about in international journals. It is just the governments have decided to segment it off. I hate to say it, but maybe even the E.U. could tell us something about how we should do this better.

We would like to hear from you and hope the collaboration will continue, but thank you very much for your testimony.

The hearing record will remain open for 10 days. Members may submit additional information for the record within that time.

If there is no further business to come before the Subcommittee, it stands adjourned.

[Whereupon, at 3:36 p.m., the hearing was adjourned.]

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