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Witness appearing before the U.S. Senate Committee on Health, Education, Labor and Pensions

Treating Rare and Neglected Pediatric Diseases: Promoting the Development of New Treatments and Cures

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INTRODUCTION

Good afternoon Chairman Harkin and Members of the Committee. My name is John F. Crowley of Princeton, New Jersey. I am the Chief Executive Officer and Chairman of Amicus Therapeutics, Inc. and I serve on the Board of Directors of the Biotechnology Industry Organization (BIO). More importantly, I am the father of two children diagnosed in 1998 with Pompe disease - a rare and devastating neuromuscular disorder. I appreciate the opportunity to be here today to talk about ways in which the federal government can encourage and speed the development of drugs, vaccines, and diagnostic tests for rare and neglected diseases.

Amicus Therapeutics is a 100-person biopharmaceutical company developing orally administered, small molecule drugs called pharmacological chaperones, a novel, first-in-class approach for treating a broad range of human genetic diseases. Amicus' lead program is in Phase 3 testing for the treatment of Fabry disease, a rare and severe lysosomal storage disease affecting an estimated 10,000 individuals worldwide. My involvement with the biotechnology industry stems from that 1998 diagnosis of our two youngest children, Megan and Patrick.

BIO represents more than 1,200 biotechnology companies, academic institutions, state biotechnology centers and related organizations across the United States and in more than 30 other nations. BIO members are involved in the research and development of innovative healthcare, agricultural, industrial and environmental biotechnology products, thereby expanding the boundaries of science to benefit humanity by providing better healthcare, enhanced agriculture, and a cleaner and safer environment.

From my perspectives as both a biotechnology entrepreneur and as a father, I am most appreciative that the Committee is undertaking this broad inquiry into the state of rare and neglected pediatric diseases. The time to consider change and to build on past successes could not be better. We have come a long way but we have much further to go to address the severe unmet medical needs of people who bravely live with these rare diseases, especially children. Research and drug development in this crucial field is at a precarious tipping point.

The Foundation of Success: The Orphan Drug Act

The Orphan Drug Act (ODA) of 1983 has brought unprecedented success. It contained several market based incentives for biotechnology and pharmaceutical companies to develop and market products for rare diseases. To date, in excess of 1,000 orphan product designations have been granted by the FDA's Office of Orphan Product Development and more than 250 drugs and biologics have received approval by the FDA with Orphan designation, collectively helping millions of adults and children with rare diseases worldwide. We have come a long way, indeed. In the decade prior to enactment of the ODA fewer than ten products for rare diseases came to market. Among these advancements are accomplishments that I have participated in professionally and, in the case of my own children, have witnessed most personally. Today, there are an estimated 7,000 rare diseases, each one affecting 200,000 or fewer individuals, but collectively affecting nearly 30 million Americans. Treatments exist for only a fraction of these devastating, life-threatening diseases leaving so many people of all ages with significant unmet medical needs. And of those treatments, the majority of approved orphan drugs are for those rare diseases with higher prevalence.

BIO believes that the lesson we can learn from the ODA is that government policies can effectively foster research and development of products for rare diseases – and create an entirely new marketplace to meet severe unmet medical needs. The challenges of developing orphan products are great and they require innovative policy and regulatory solutions. Further, many rare diseases affect far fewer patients than the 200,000 threshold in the ODA. For these diseases, the challenges are even more daunting.

Continued Unmet Medical Need

The gap in development for pediatric rare diseases is particularly acute for the most uncommon disorders, which collectively still affect the majority of children with rare diseases. Most all rare or orphan diseases with lower prevalence remain without treatment. According to an Orphan Drug Development Trends report published by BioMedical Insights in January of this year, 83% of rare diseases are "ultra-rare", yet only 11% of orphan designations issued between 1997 and 2009 were for these ultra-rare diseases (144/1,310). What do these numbers translate to for the average patient family in the rare disease community? No treatment options and the invariable and painful words from a physician that are all too common: "I am sorry. There is nothing we can do. There are no treatment options for your child."

For most of these rare and extremely rare diseases, perhaps as many as 2/3, medical research is absent – completely. Affected patients, their families and friends strive to bring attention to their causes. For other diseases, such as Tay-Sachs, for example, medical research is just now gaining momentum, despite it being one of the most commonly known rare, genetic diseases, with one of the oldest advocacy groups in the country, and the first disease for which a carrier genetic test was perfected back in 1970. Yet it could be many more years before a safe,

effective treatment is ready for the clinic, and tens of thousands of children and adults will still die from this deadly neurodegenerative disease. As a past-president of the National Tay-Sachs & Allied Diseases Association, I've seen the hope sustained by parents listening to academic researchers, while they watch Tay-Sachs ravage their young children physically and mentally. And for those rare diseases fortunate to have a treatment, not all is perfect. As can be the case with Pompe disease, for example, many patients cannot tolerate the treatment due to immunogenicity or other significant issues. For others, the treatment may be of limited effectiveness but there are no other options. Much work remains to be done in orphan drug development to evolve the unmistakably critical work already achieved for rare diseases.

Ability to Meet the Challenges

In the year 2010, we have the collective ability to tackle the challenges of understanding and developing viable treatment options for rare and ultra-rare diseases with unmet medical need, especially for children. Basic scientific, biomedical and preclinical research is taking place with groundbreaking technology in laboratories at colleges and universities, independent academic medical centers, at the National Institutes of Health, and in the biotechnology industry. Initiatives such as the Therapeutics of Rare and Neglected Diseases (TRND) Program at the National Human Genome Research Institute (NHGRI) have impressive capabilities and hold great promise for discovery at the level of public/private collaboration that is necessary to help address these many of these challenges. In particular, this is a new and exciting approach to moving forward from screening and developing compounds through the junctures of pre-clinical and clinical work, optimizing resources and harnessing the varied expertise of collaborators along the way.

Though just getting off the ground, the TRND program has the potential to help companies bring promising products forward. Many of these products stall in development because biotech companies lack the financing to advance them. The TRND program could fill some of these funding gaps. BIO is encouraged by this effort. We pledge to work with the NIH on intellectual property concerns, technology transfer rules, and other matters to make sure the program accomplishes its goals.

Patient advocacy for pediatric rare diseases is increasingly important. Families and friends of children and adults affected by these debilitating, horrific, often fatal rare diseases no longer passively sit around sick rooms and hospital rooms. They – we, because I am one of them, are well aware of the promising developments taking place in the research labs of the biotechnology industry and at academic institutions and are confident that technology can match our sense of urgency. Patient advocates are proactive agents for changing how this research can be conducted and how quickly it gets translated to the clinic, all with the hope that it will positively influence their loved one's clinical outcome. Today's patient advocacy and disease organizations are partners in social and venture philanthropy with industry. They want the exciting and promising technology that exists for their diseases to see the light of day, and even more they want treatments and potential cures to be realities in their lifetimes. Here are just two examples.

The Cystic Fibrosis Foundation is one such health venture philanthropist. In 2000, there were few potential treatments in the CF pipeline. Today, there are more than 30 treatments in development, a few already available to patients, with a pipeline portfolio ranging from gene therapy, protein rescue, mucus alteration, restoring airway surface liquid (ion transport), anti-inflammatory, anti-infective, transplantation and nutrition. In the area of protein rescue alone, the CF Foundation invested more than $100 million with Vertex Pharmaceuticals and $25

million with PTC Therapeutics, both fellow BIO member companies, for two different small molecules in the past few years.

"Fight Spinal Muscular Atrophy" (FightSMA) dedicates itself to research for a cure for this group of diseases which affect the motor neurons of the spinal cord and brain stem. In its infantile form, SMA kills more babies than any other genetic disease. With grants up to $250,000 each, FightSMA is a social philanthropy funding about 20 academic and medical institutions in the US and internationally. The organization brings approximately 25 SMA researchers together for an annual scientific conference to encourage collaboration at the same time that SMA-affected families come to meet each other for support and learn from these researchers.

It is exactly this type of community-driven, cross-fertilization and financial support of ideas, and sharing of disease experience that has occurred at advocacy organization conferences for years that the patient community is more recently asking take place on a broader scale in clinical research and drug development. Patients are appreciative of the active role of the Office of Rare Diseases at NIH in supporting these meetings and of the Office of Orphan Product Development participation at many programs. Collaborative approaches are in the US and abroad, originated by highly respected organizations such as NORD and now assumed by their counterparts, such as EURORDIS, CORD and ICORD. The 2010 European Conference on Rare Diseases held last month in Krakow, Poland, attracted more than 600 participants from 43 countries, with one-third from Eastern Europe: the aim to discuss public policies and actions that will improve the lives of people with rare diseases. The rare disease community may be growing, but it represents a world that is getting smaller all the time. The demands of the diseases themselves have always been there; however, the presence of the diseases is augmented by the fast-paced technology available to researchers, the charged atmosphere of

advocacy, immediate access to information about diseases, research and support groups, and connectivity through the Internet and social media for all disease stakeholders.

Collectively, these activities represent a trend toward acceleration of all aspects of orphan drug development to ultimately, and most importantly, benefit patients living with rare diseases. The federal government can support new policies and programs that extend, leverage and enhance these global efforts.

The biotechnology industry has made a significant contribution to this field over the years. Indeed, the mission of many biotech companies, such as my own, is to bring hope to the patients who suffer from rare diseases. Today, I would like to provide you with some thoughts about policies that will complement and advance the objectives of the ODA and facilitate the development of the next generation of orphan products for children.

NEW POLICIES FOR CONSIDERATION TO ACCELERATE TREATMENTS FOR RARE AND NEGLECTED DISEASES

Changing the FDA Regulatory Environment for Pediatric Rare Diseases

The Committee must address the current regulatory environment and the FDA's review process for orphan products. For instance, the sheer size of patient populations is an important factor for consideration in clinical study design. Affected individuals are part of such small individual patient populations; they may represent disease prevalence of as many as 67:100,000 to as few as 2:100,000. No one rare disease exceeds an incidence of 200,000 in the US. Limited individual disease experience makes it unlikely that there are organized registries from which to

draw information for the majority of these diseases, and unrealistic to consider conducting natural history studies as prelude to or in parallel with clinical trials. (The topic of disease and product registries currently is a controversial one in the rare disease community and one worth exploring, as well.) Numbers of subjects for any orphan product study should be carefully considered based on current disease situations. Given that these trials, especially registration studies requiring larger numbers of subjects, typically necessitate global recruitment, protocols should be able to satisfy institutional review boards and ethics committees internationally. In the ultra-rare category, consideration also should be given to combined Phase 1/2 and Phase 2/3 studies with a Phase 4 commitment from sponsor companies making these investments. The regulatory mantra should be: Approve fast, follow long.

The Committee should respectively consider enabling the FDA to focus on orphan diseases/orphan products beyond the fine work already being conducted by the Office of Orphan Product Development. The multi-systemic, complex nature of the majority of rare diseases, as genetic, metabolic, inborn errors of metabolism, further complicates a simple route forward for the guidance and development of well-designed clinical protocols. Therefore, study design guidance and review for rare diseases should also have an approach characteristically distinct from that used with common disease guidance and review. The FDA would benefit from a dedicated team of experts in the genetic and metabolic disorders that together with regulatory colleagues can offer guidance to study sponsors that will result in clinical protocols that account for limited patient numbers, the most current collective thinking on disease biomarkers, surrogate endpoints and better use of pharmacogenetics.

I suggest that the establishment of a separate **Division of Genetic and Metabolic Disorders at FDA** is essential and long overdue. Along these same lines, the agency might consider having reviewers, staff other than OOPD, spend more time with rare disease patient

organizations to learn from their leadership and members what they think and know of clinical trials, barriers to participation, etc. This might be mutually beneficial for educational purposes and understanding the rare disease patient experience.

Additionally, BIO urges FDA to publish further guidance regarding orphan drug development that provides interpretation of current regulations including: what are acceptable subsets of disease to meet the prevalence requirement; what is a "major contribution to patient care" that allows a drug to be found "clinically superior" even if it has the same active moiety of a previously approved drug; what is the definition of "reasonably likely to predict clinical benefit", and whether the sponsor of the original drug can also be a "subsequent sponsor."

Other regulatory changes should be pursued as well. For example, we urge that FDA review use of its standards for demonstrating efficacy of a rare disease product. The requirement for sponsors to use two adequate and well-controlled studies is the same standard used by the agency for other drugs and biologicals. However, it is significantly harder to develop those studies for rare disease products because of the small patient populations available. This is particularly true for very rare diseases. BIO urges FDA to consider alternatives that include: approval based on a single adequate and well controlled trial at a $p \leq .05$, if there have been NIH-conducted studies using the same populations; use of consortia between government, academia and industry; and use of patient registries for rare diseases as part of efficacy considerations.

In addition, we urge FDA to support greater use of surrogate endpoints for product approval, either for full approval or accelerated approval purposes. Although they currently can be used during the accelerated approval process, more guidance from the agency is needed on use of surrogate endpoints for registration. Amazingly, in the past 20 years, only one drug for the

treatment of a human genetic disease was approved under the "accelerated approval" provision of subpart H of the FDA regulations.

Moreover, BIO believes FDA can improve communications processes for rare disease stakeholders. For example, once orphan designation has been granted, there is no communication policy for sponsors as the review divisions take over. This often makes interaction with the agency difficult. It is important that FDA encourage reviewers to establish communications processes that allow reviewers and sponsor researchers to discuss scientific issues based on real-time data more efficiently. Such real-time scientific dialogue would not take the place of the required regulatory communications and meetings with FDA but rather ensure that these required communications and meetings are utilized more efficiently. Additionally, there is no special priority given to rare disease products in current FDA practices regarding protocol assistance, communication with the agency and other matters. Given the complexity and special challenges of developing rare disease products, these communication gaps impede development and approval.

Other regulatory changes should be pursued as well, such as greater transparency at the agency including more meeting opportunities, and greater consistency among FDA's review divisions. The challenges of developing rare disease products require new regulatory approaches. Also, in light of the fact that biomedical research and development is a global enterprise, we urge the FDA to work with foreign regulatory agencies, particularly in Europe, to harmonize requirements for pediatric research.

In addition, many patients suffering from rare diseases are treated by products that are labeled for another indication. Companies looking to get FDA approval for the rare disease indication are often either prohibited or severely restricted from performing a placebo-controlled trial for

that indication because the commercially available (off label) product has become the clinical standard of care. In such situations, FDA should allow non-placebo controlled trials such as historical control or open label trials.

Regarding FDA's approval of medical devices for rare diseases, the use of different threshold numbers for defining rare ("orphan") disease for medical device (4,000) versus drugs and biologics (200,000) is illogical. The device regulations should be changed, as it is the disease incidence not the therapy that should define the population.

Finally, we note that the dual statutes governing pediatric research, the Best Pharmaceuticals for Children's Act (BPCA) and the Pediatric Research Equity Act (PREA), have been remarkably successful in ensuring that the medications used in children are tested and labeled appropriately for their use. Together BPCA and PREA have generated a wealth of pediatric drug information for physicians and parents. BPCA rewards drug companies with 6 months of additional market exclusivity after the completion of studies in children as requested by the Food and Drug Administration (FDA). PREA requires new drugs to be studied in children and allows FDA to mandate child studies in certain already marketed drugs. However, despite a proven track record in encouraging pediatric medical research, both programs are scheduled to expire in 2012. BIO urges Congress to recognize the success of these programs, eliminate the sunset provision, and make permanent the incentives for ongoing pediatric research.

Understanding and Accepting Appropriate Risk Tolerance

The required pre-clinical and clinical safety studies and risk assessments for the development and approval of live saving pediatric drugs for rare diseases is virtually the same in all instances

as for antibiotics for common ear infections. We need to better understand the risk/reward ratios for these rare diseases drugs. Addressing the tolerance for risk in drug development in the rare disease space is also essential to advancing newer therapies. Individuals directly affected by these highly unusual disorders, or their parents, custodial family members and caregivers are experiencing unusual, almost unique and unprecedented unmet need. They have a sense of urgency few if any can understand, but this does not necessarily cloud their judgment or ability to understand the risks and benefits of clinical trial participation. There should be no less scrutiny of safety for patients with ultra-orphan diseases but many of the traditional pre-clinical and clinical safety studies typically required of most drugs need to be reevaluated in the context of the cost and time associated and the severity of the unmet need.

Certainly, the protracted timelines too often impose the ultimate cost on affected families awaiting treatment for their rare disease...the loss of their child or other loved one. It behooves the FDA to reassess the process and the extraordinary financial costs involved in developing orphan drugs. For example, the last five drugs developed and approved to treat lysosomal storage diseases have cost more than $200 million each in research and development expenses alone to develop, while addressing populations in the US of less than 3,000 patients. Each of these drugs were for use in children as well as adults. There is no current economic framework that exists to promote this kind of investment. While the industry is appreciative of the existing incentives established by the Orphan Drug Act 27 years ago, it is time to update these to ensure ongoing and future innovation to benefit rare diseases. Some very practical considerations are: investment tax credits, permanent R&D credits and tax grants for companies conducting research for ultra-orphan treatments, accelerated clinical studies, and special tax treatments for investments in smaller companies with fewer than 250 employees.

BIO companies believe that FDA has made great strides to make sure that safe and effective orphan products reach patients as soon as possible. For example, we applaud the FDA Office of Orphan Products Development for their sponsorship of the training program for reviewers on statistical methods for small patient populations. In addition, the "Build an Orphan" – designed to help companies properly submit the application for orphan drug designation in a timely fashion – holds promise. But more must be done.

The ODA created a grant program administered by the FDA to fund companies for development of orphan products. It's called the Orphan Drug Grant Program. This program has not had increases in funding commensurate with inflation for many years. BIO urges increased funding for the Orphan Drug Grant Program.

Similar to what FDA has done through its Critical Path initiative, we believe the agency also needs to take affirmative steps to spur drug development for rare diseases. The regulatory approval pathway simply must be more predictable. For example, during the most recent negotiations surrounding enactment of the Prescription Drug User Fee Act (PDUFA), the FDA committed to developing a series of guidances regarding clinical trial design; adaptive clinical trials; and new methods of statistical analysis. These would be valuable for developers of rare disease products. We appreciate the publication of the adaptive clinical trial guidance and the non-inferiority draft guidances released earlier this year, and we look forward to timely publication of other pending guidances on clinical trial design.

Fund the Cures Acceleration Network

The recently enacted Patient Protections and Affordable Care Act (PPACA) includes a provision called the Cures Acceleration Network (CAN) that is intended to speed the translation and application of promising new treatments for diseases from the laboratory to the marketplace. The CAN will be placed under the Office of the Director of NIH, and is authorized to make grants through the NIH to biotech companies, universities, and patient advocacy groups to target applicants that have shown promise at the laboratory level, but have not been able to advance enough to attract investors that are willing to commit to a promising discovery.

Specifically CAN will focus on funding the development of "high need cures", defined as those which the NIH Director determines to be a priority to "diagnose, mitigate, prevent or treat harm from any disease and condition" **and** for which commercial incentives are unlikely to result in timely development. The functions of CAN will be to not only support research that would accelerate the development of high need cures, but to reduce barriers of getting discoveries that are in the lab into clinical trials, as well as facilitate the FDA review process.

In regards to providing assistance with the FDA review process, CAN will work to facilitate communications with the FDA on the status of a high needs cure approval and ensure activities are coordinated in a manner that would expedite their development approval. Lastly, CAN will work to connect those developing high need cures with additional technical assistance.

PPACA authorizes $500 million for FY 2010 for the creation of two new grant programs. Importantly, these grant awards will be available to biotech companies, medical centers, universities, disease advocacy organizations, patient advocacy organizations, pharmaceutical companies and academic research institutions.

Extend and Expand the Qualifying Therapeutic Discovery Project Tax Credit

One provision included in the health reform law that may be of enormous benefit to small life sciences companies is the Qualifying Therapeutic Discovery Project Credit program, now Section 48D of the tax code. Modeled after existing tax credits for investments in advanced renewable energy efforts, this program creates $1 billion of tax credits or grants to encourage investments in promising new therapies to prevent, diagnose, and treat acute and chronic diseases. For qualifying companies with 250 employees of fewer, this program will provide immediate funding for work on therapies for cancer and other debilitating conditions, including a number of rare diseases, while providing small firms the ability to weather the ongoing economic storm. Without help to these companies, the effects of the financial crisis and the resultant capital markets contraction threatens to halt or significantly delay the next generation of promising therapies for various diseases and afflictions that affect tens of millions of patients and their loved ones.

Today, July 21, is the deadline for applications for the therapeutic credit program. While Congress saw fit to fund this program with $1 billion, the Treasury Department has estimated that more than 1,000 applications could easily be filed. In reality this number could be closer to 2,000. Whatever the number of applications, it is clear that there will be many more promising projects than can be funded under the initial $1 billion.

CONCLUSION

I agree with President Obama' statement that "science is more essential for our prosperity, our security, our health, our environment, and our quality of life than it has ever been before . . .

including [the] creat[ion of] new incentives for private innovation [to] promote breakthroughs in energy and medicine."

Change does not come easily. It was not an easy process when a group of parents lead by Abbey Meyers, the founder of NORD, spearheaded the development of the Orphan Drug Act in 1983. In January of 1984, when Ronald Reagan signed the Orphan Drug Act into law, with Democrats and Republicans at his side, he stated that: "I only wish that with the stroke of this pen that I could also decree that the pain and suffering of people living with these diseases would cease as well." It didn't, but the Act did create an environment with a system of special incentives for industry and certain government supported programs that spawned a new era of research and drug development. We have come very far in that last quarter of a century but we have much further to go. The change brought about by the Orphan Drug Act improved millions of lives in this country and abroad, helped launch an industry and established the global rare disease advocacy movement. It does not come easily for every family that struggles with illness and then receives a life-altering diagnosis of a rare disease with no treatment or cure. But each of us committed to orphan drug development, including the FDA and those responsible for seeing the agency is appropriately funded, owe those families a more-than-fighting chance that their medical needs will be met- and that more and more parents will instead receive a diagnosis of a rare disease in their child, followed immediately by the words: "There are, however, several treatments options for your child."