PhRMA Statement for the IOM Committee Accelerating Rare Disease Research and Orphan Product Development

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According to the National Organization for Rare Disorders, there are nearly 7,000 diseases that are considered rare. Rare diseases are defined by the U.S. Orphan Drug Act (ODA) as those that affect 200,000 or fewer people in the United States. Although individually these diseases are not highly prevalent, nearly 30 million Americans, 1 in 10 of the population, have a rare disease. Rare diseases often have a complex etiology and can be difficult to characterize frequently resulting in misdiagnosis and non-treatment. Because of advances in medical science, researchers have developed assays and tools to determine the molecular and genetic causes of a number of rare diseases leading to the approval of new treatments for these conditions. Diseases which were previously untreatable and life threatening now have medicines to significantly improve and prolong the life of a patient. In particular, treatment of rare diseases in children can have a profound impact on their chance of survival and development into a functioning adult. The biopharmaceutical industry has made significant advances in the discovery and approval of new medicines for rare diseases such as Gaucher disease, myelodysplastic syndromes, enzyme deficiencies, and rare cancers and continue to invest in research for these diseases. Despite the advances in drug development so far, the impact of rare and orphan diseases on public health in the U.S. and globally continues to drive the need for medical innovation and increased resources targeted towards drug discovery and development for these disorders. Accelerating rare disease research and product development may also help pave the way for future innovation in the treatment of more common disorders. The knowledge derived from rare disease research may facilitate the development of more targeted therapies for more widespread afflictions such as neurodegenerative disorders.

In response to the need for rare disease treatment, the U.S. Orphan Drug Act was established in 1983 to provide incentives for sponsors to develop products for rare diseases. These incentives include market exclusivity, tax credits, and grant programs which have successfully stimulated company investment in research and development for treatments for rare diseases. Prior to 1983, fewer than 10 products for rare diseases were approved. Since the ODA’s inception, 344 drugs have been approved providing innovative medical treatments for over 12 million Americans in the United States. The U.S. FDA Office of Orphan Products Development (OOPD) oversees the administration and adoption of the ODA’s provisions and promotes research into the development of orphan drugs. As part of OOPD’s mandate, the FDA confers a particular status, referred to as an orphan designation, to qualify the sponsor for the incentives of the ODA. Since 1983, OOPD has granted 2,085 orphan designations to sponsors and in the past nine years, the number of requests for orphan designations has nearly doubled. In 2008, OOPD granted 166 orphan designations resulting in the highest number of orphan designations in a single year. According to the FDA, the Orphan Drug Act has stimulated investment in orphan drugs and both orphan designations and approvals have continued to experience upward growth since 1983. Supported by the success of the ODA and increasing breakthroughs in medical innovation, biopharmaceutical companies have stayed committed to fighting for rare diseases treatments.

Despite the vast advancements of science, there are still many challenges researchers must face in developing drugs for rare or orphan diseases including clinical trials for small
patient populations, difficult patient recruitment and enrollment across widespread geographical locations, as well as the need for specialized training for both the clinical researchers and Regulators. The majority of New Drug Applications received by the FDA for orphan drugs have clinical trials based on low patient numbers, some as small as 20 patients. The approval of a drug to treat pediatric Pompe disease for example was based on a pair of clinical trials that in combination enrolled 39 patients from around the world at eight different clinical trial sites. The drug had been shown to significantly improve survival in infants with Pompe disease compared to those at historical baseline. Without treatment, Pompe disease is a debilitating, progressive and often fatal disorder affecting fewer than 10,000 people worldwide. People born with Pompe disease have an inherited deficiency of an enzyme known as acid alpha-glucosidase (GAA) and most patients experience premature mortality due to respiratory failure. Today, hundreds of patients in more than 30 countries are receiving treatment for Pompe disease and are experiencing great improvements in the longevity and quality of their life. The researchers of Pompe disease treatment overcame the hurdles of clinical trial designs to receive approval by the FDA and as well as other regulators authorities worldwide.

The recruitment of patients in the Pompe disease clinical trials would not have been possible without the assistance of a patient advocacy group to recruit the 39 patients globally. Patient advocacy groups and other patient networks have played a significant role in the advancement of investigational drugs for rare and orphan diseases into clinical trials and regulatory approval. Patient advocacy groups help their members by sharing resources and information amongst patients and family members, assist researchers by allowing for easier access to patients, resulting in higher numbers recruited and enrolled into clinical trials, and also perform innovative research for specific diseases. These patient organizations function on both a national and international level and in conjunction with other international patient groups to provide support, share information, and allow access to patients globally. Patient recruitment for clinical trials in a disease that affects small number of patients globally can be a large hurdle for researchers. However, they can benefit greatly from collaboration with patient advocacy groups and other patient organizations.

Clinical scientists and regulatory reviewers involved in rare disease research require specialized training distinct from the skill set of researchers focused on common disorders. Clinical scientists must learn to adapt clinical trial design to be relevant to smaller patient populations often with modified or composite endpoints. In addition to training researchers, regulatory reviewers must be trained in novel clinical trial design methodologies in order to determine if a clinical study shows acceptable clinical safety and efficacy with a more limited data set. In addressing this issue, the FDA has recently implemented internal courses focused on the science of small clinical trials. The courses are intended to focus on alternative study design methodologies such as adaptive designs, Bayesian approaches, and enriched patient populations in order to better educate the FDA and sensitize regulatory scientists to the possibility of diverse approaches by applicants. Through these courses, regulators will be trained in novel clinical trial design for rare diseases to best determine if a study has met approval standards.

In addition to the unique challenges of clinical trial design, patient recruitment, and specialized training for rare diseases, orphan drug applicants also face the same obstacles of drug development for prevalent diseases and must meet the same evidentiary standards for FDA approval. As with investigational drugs intended to treat common diseases, 80-90% of
drugs that enter into clinical trials fail during drug development.1 In most cases, this is due to preclinical toxicity, lack of efficacy, or clinical safety issues that lead to the termination of drug development. Therefore, receiving orphan designation status does not guarantee meeting regulatory standards for market approval since it is often based on preliminary but promising data early in the development process. Researchers involved in the discovery and development of orphan drugs must find a way to address both the challenges of drug development shared with common disorders and those unique to rare diseases. The biopharmaceutical industry approaches rare disease drug development with the same rigorous scientific and regulatory standards as more prevalent diseases and continues to investigate and pursue novel methodologies to address these drug development barriers. A key to successful rare disease drug development is collaboration between advocacy organizations, private foundations, research institutions, medical institutions, Federal agencies, and the biopharmaceutical industry. These collaborations allow for coordination and shared access of existing resources, integration of clinical, regulatory and product development expertise, and identification of where overall gaps and barriers in development exist. Oftentimes, these collaborations involve multiple institutions and multiple locations internationally. Without the strengths of all outside stakeholders working in collaboration and helping to facilitate rare disease research, many of the treatments and successes of rare disease research would not exist today. Recognizing the importance of collaboration and the high failure rate of drugs in preclinical development, the National Institutes of Health launched in May 2009 the first integrated drug development pipeline to produce new treatments for rare and neglected diseases called the Therapeutics for Rare and Neglected Diseases program (TRND). TRND is intended to stimulate research collaborations by working with rare disease experts in academia and disease oriented foundations to move compounds through preclinical development and then further collaborate with pharmaceutical and biotech companies to conduct the clinical trials.8 NIH Office of Rare Diseases Research (ORDR) will be responsible to oversee the progress of TRND. Again recognizing collaboration is a critical element of rare diseases research, the NIH announced in October 2009 the expansion of the Rare Diseases Clinical Research Network including funds for 19 research consortia.9 The RDCRN addresses the challenge of small patient numbers in one geographic location by facilitating collaborations among scientists in order to share access to geographically distributed research resources and establish training programs for clinical investigators in rare disease research. Collaborations amongst industry, patient organizations, academia, Federal agencies, and other organizations involved in finding treatments for rare diseases is necessary to address the unique challenges of rare disease drug development.

Biopharmaceutical companies have stayed committed to fighting for treatments for rare diseases. In order to address how we can collectively find solutions to impediments in drug discovery and development, the Pharmaceutical Research and Manufacturers of America (PhRMA) has convened a Rare and Specialty Disease Committee. This Committee will work in collaboration with outside stakeholders, to decrease the barriers that impede development with the goal of bringing innovative products to patients earlier. The Rare and Specialty Diseases Committee was chartered in the Fall of 2009 and is in the process of shaping its mission and vision. We welcome this forum as a way of identifying barriers to the development of new treatments for rare diseases.
3 PhRMA. Orphan Drugs in Development for Rare Diseases. 2007 http://www.phrma.org/files/Orphan%202007.pdf (accessed 23 October 2009)