September 30, 2019

Division of Dockets Management (HFA-305)
U.S. Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Re: Docket No. FDA-2014-D-1461: Rare Pediatric Disease Pediatric Priority Review Vouchers; Draft Guidance for Industry

Dear Sir or Madam,

The Muscular Dystrophy Association (MDA) thanks the Food and Drug Administration (FDA or "Agency") for the opportunity to comment on the Agency's draft guidance entitled "Rare Pediatric Disease Pediatric Priority Review Vouchers; Draft Guidance for Industry."

MDA is the nation's leading nonprofit organization dedicated to transforming the lives of individuals living with muscular dystrophy, ALS, spinal muscular atrophy and other neuromuscular diseases through innovations in science and innovations in care. MDA fulfills its mission by funding biomedical research, by providing access to expert clinical care and support through its national MDA Care Center Network which is comprised of expert medical clinics at more than 150 of the top health care institutions across the US, and by championing public policies and programs that benefit those we serve. Since inception, MDA has invested more than $1 billion in research grants to accelerate treatments and cures for neuromuscular disorders, making MDA the largest source of neuromuscular disease funding in the U.S. outside of the federal government.

All neuromuscular diseases (NMDs) are progressive in nature with symptoms ranging from mild to life-threatening. While a robust therapeutic development pipeline exists for NMDs, drug development remains challenging, and only a handful of treatments have been approved by FDA for NDMs.

NMDs are varied in their symptomatic onset, severity, manifestation, and progression. Some NMDs are typically first symptomatic in adulthood, such as amyotrophic lateral sclerosis (ALS) and oculopharyngeal muscular dystrophy (OPMD). Others manifest with symptoms in infancy or childhood, such as spinal muscular atrophy (SMA), Duchenne muscular dystrophy (DMD) and Friedreich's Ataxia (FA). The heterogeneous nature of many NMDs bring additional challenges in developing therapeutic options to treat these conditions. While recent innovative therapies for

SMA and DMD certainly serve as counterexamples, pediatric NMDs and NMDs that span both pediatric and adult populations have witnessed a scarcity in therapeutic development. There are still many NMDs with pediatric populations that are awaiting their very first treatment.

Consequently, MDA is supportive of programs that help incentivize the biopharmaceutical industry to develop therapies for rare pediatric diseases. MDA supports the Rare Pediatric Disease Priority Review Voucher (RPD PRV) program and advocated for its reauthorization and reform as part of the 21st Century Cures Act. Since 2016, four priority review vouchers have been awarded to neuromuscular disease therapies. Our hope is that the RPD PRV program will continue to incentivize biopharmaceutical companies to develop therapies for both these and other neuromuscular diseases with pediatric populations.

Please find specific comments regarding the guidance below:

Definition of a Rare Pediatric Disease

As the Agency is aware, there was concern voiced within the patient community with the Agency's interpretation of the previous statutory definition of a rare pediatric disease. Under that interpretation, a rare pediatric disease was recognized as any rare disease in which more than half of the population is under 18 years of age.[1] Under this definition, several NMDs with pediatric populations could be excluded from the program, including, for example, some forms of SMA and muscular dystrophy. Additionally, as care improves for individuals and as more individuals are living beyond age 18, some disorders previously defined as pediatric diseases could be in a position to no longer qualify, which was concerning to many in the NMD community who appreciate the stimulus effect of the designation.

In an effort to ensure that the broadest application of a pediatric disorder was deployed for purposes of the Act, MDA supported the amended definition of a rare pediatric disease in the 21st Century Cures Act (P.L. 114 – 255) as it successfully reoriented the definition away from a purely prevalence-based assessment to one that considers when the life-threatening manifestations of the disease are occurring. This new definition would be more inclusive of a wider array of disorders with severe pediatric implications.

Consequently, we are generally supportive of the proposed implementation of the updated definition of a rare pediatric disease. FDA shows flexibility in its assessment of what constitutes a "serious or life-threatening" manifestation using standard-of-care as the baseline scenario. Additionally, while we have concerns with a purely prevalence-based assessment for the proportion of children versus adults with the life-threatening manifestation, we understand this is largely dictated by the statute, and therefore recognize that our concerns in this regard are not with the interpretation employed by FDA.

[1] Rare Pediatric Disease Priority Review Vouchers, Draft Guidance for Industry; Availability, 79 FR 6845 November 17, 2014)

MDA requests clarification from FDA regarding situations similar to the cited example in footnote 13.[2] FDA cites cystic fibrosis (CF) as an example of a disease that presents serious and life-threatening manifestations that primarily affect children while also presenting serious and life-threatening manifestations that do not primarily affect children (e.g. impaired lung function). Under this construction, if a sponsor sought an RPD PRV for an intervention that treats impaired lung function in children with CF, and successfully meets all other regulatory requirements, the query arises as to whether the sponsor would be awarded the voucher even though impaired lung function is not the manifestation that qualifies as a serious or life-threatening manifestation that primarily affects children. Such ambiguity could have a chilling effect on development.

To take this same example one step further, in the aforementioned scenario, the question may also arise as to whether a sponsor would be eligible for a RPD PRV for a therapy that treats a non-serious and non-life-threatening manifestation primarily affecting children if the disease still qualifies as a rare pediatric disease due to the presence of a serious or life-threatening manifestation primarily occurring in children.[3] If the sponsor is able to receive a voucher in this manner, sponsors could be awarded vouchers for therapies that do not necessarily treat serious and life-threatening manifestations that primarily affect children. The community would benefit from additional clarity from FDA on situations such as those set out in this example.

Inclusion of Adults:

MDA supports the Agency's proposal to allow for voucher eligibility if the therapy is concurrently developed for adults while also being developed for children. There are NMDs that affect both pediatric and adult populations, and it would not be in the best interest of the neuromuscular community for sponsors to be disincentivized (whether real or perceived) from testing investigational therapies in adults. We appreciate the Agency's recognition of this potential concern and therefore conclude that testing in adults should be allowed to concurrently occur while preserving voucher eligibility. MDA also supports the Agency's proposal to allow for concurrent approval of a therapy in adult and pediatric populations while preserving voucher eligibility.

Resources for Administering the Program:

MDA believes that a well-resourced FDA is critical to the health and well-being of the neuromuscular community. Consequently, MDA seeks to ensure that the RPD PRV program does not serve as a resource burden for FDA, and FDA is adequately and appropriately funded to fully implement the RPD PRV program without jeopardizing any other programs important to

[2] Footnote 13 reads, "That is not to say that manifestations that primarily affect adults cannot also be serious or life-threatening in children. But based on the statutory definition, FDA is required to determine which manifestations primarily affect children and which primarily affect adults. For example, FDA has determined that impaired lung function is a serious or life-threatening manifestation of cystic fibrosis that primarily affects adults, but can also be serious or life-threatening in children. FDA considers cystic fibrosis to be a rare pediatric disease based on other manifestations of the disease that do primarily affect children."

[3] To describe it differently, disease X presents with two symptoms that primarily affect children: one is serious and life-threatening, the other is not. Can the sponsor still seek a voucher if the therapy treats the non-serious symptom and not the serious symptom?

our nation's public health. We hope the user fees associated with the program adequately compensate FDA for the additionally-awarded priority review.

While we hope the review divisions tasked with the additional priority reviews are adequately resourced through the user fee, we are concerned that the Office of Orphan Product Development (OOPD) and Office of Pediatric Therapeutics (OPT) who are tasked with assessing eligibility of products for the RPD PRV as well as RPD designations and PRD product application designations, will similarly receive additional resources for their efforts. Both offices serve critically important functions for rare and pediatric disease patients, and the added resources associated with the program shouldn't only go to review divisions. Instead, MDA requests that all FDA offices associated with administering the program are adequately resourced to do so.

Revocation of Vouchers:

MDA is aware that with a program such as the RPD PRV program, there is always opportunity for misuse and misapplication, and is, therefore, supportive of interventions that will help ensure this incentive remains targeted in scope and applied in a manner consistent with the intent of Congress. MDA is concerned with any possible abuse of the RPD PRV program, and strongly encourages FDA to use its statutory abilities to ensure any therapy awarded a voucher is actually treating rare pediatric disease patients.

We look forward to working with the Agency to ensure robust development of rare pediatric disease therapies for neuromuscular diseases continues and accelerates. For questions regarding MDA or the above comments, please contact advocacy@mdausa.org.

Sincerely,

Paul Melmeyer, MPP
Director of Regulatory Affairs