Putting Patients First

Recommendations to speed responsible access to new therapies for Duchenne muscular dystrophy and other rare, serious and life-threatening neurologic disorders

Parent Project Muscular Dystrophy

LEADING THE FIGHT TO END DUCHENNE

Parent Project Muscular Dystrophy Advisory Committee on Policies to Promote Responsible Access to New Therapies

Parent Project Muscular Dystrophy (PPMD) relied on the advice and guidance of an Advisory Committee on Policies to Promote Responsible Access to New Therapies to prepare this white paper. PPMD is deeply grateful to the individuals below, who so generously offered their insights and expertise to contribute to the identification and refinement of the recommendations made in this document.

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This white paper was prepared by Julianna Belelieu of Mark Krueger & Associates, Inc. (MK&A), a consulting firm specializing in health care constituency relations. MK&A seeks to advance human health by helping clients to speed the development, approval, and appropriate use of innovative medical products and services, so that all patients have access to the best available treatment options.

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Executive Summary

There are no approved therapies indicated for the treatment of Duchenne muscular dystrophy (Duchenne), a rare, fatal genetic disorder resulting in a progressive loss of muscle function. Today, the life expectancy for patients with Duchenne is less than 30 years of age. Most patients are wheelchair-bound by age 12, and they will eventually lose function in the upper extremities and even the ability to breathe independently. As the community often states, this is not just a fatal disorder, but a disorder characterized by repeated "little deaths."

Fortunately, recent advances in science have helped to create a very robust pipeline of promising investigational treatments for this disorder. Numerous compounds are in the pre-clinical stages of testing, and at least six compounds are now in Phase 2 or Phase 3 clinical trials and approaching consideration for review and approval. Some patients are already benefiting from access to these investigational treatments, but many others – unable to meet the inclusion criteria – are left waiting.

The laws and regulations governing the evaluation process for new drugs grant the U.S. Food and Drug Administration (FDA) considerable discretion in evaluating candidate therapies for serious, life-threatening and rare disorders, such as Duchenne. The accelerated approval pathway has long served as a mechanism to respond to the need for expedited access to potentially life-saving drugs, and the 2012 Food and Drug Administration Safety and Innovation Act (FDASIA) created new opportunities to apply this approval pathway to drugs intended to treat rare disorders.

The implementation of FDASIA is an important opportunity for the Agency to promote innovative means for drug development, especially for rare disorders. In the case of Duchenne, there are particular challenges to conducting large-scale randomized clinical trials in a manner that captures a clinically meaningful benefit in a reasonable time frame. Thus, this new legislation promotes much needed changes that will facilitate the ability to gain regulatory approval for new drugs in rare diseases. Here we discuss the challenges particular to Duchenne and present suggestions for the Agency to adopt that will sharpen the focus for drug development and approval for this fatal disease.

Unfortunately, many patients and their advocates have been frustrated by the uneven application of the FDA's regulatory flexibility. To fully realize the potential to speed responsible access to new therapies for Duchenne, the FDA should:

- Expand the use of accelerated approval for therapies intended to treat rare diseases, including Duchenne muscular dystrophy.
- Issue clear guidance outlining the level of evidence required for the use of surrogate endpoints in order to expand the scope of acceptable endpoints, including novel surrogate and intermediate clinical endpoints, used to approve drugs for serious or life-threatening diseases with unmet medical need.
- Pilot the use of adaptive approval for serious and life-threatening disorders with significant unmet medical need, using existing authority under current law.
- Give greater weight to the demonstrated benefit/risk preferences of patients, as well as caregivers in the case of pediatric illness, when making risk benefit determinations. Subpart D considerations must be evaluated here, yet benefit/risk should also be addressed within the context of patients living with Duchenne.

Parent Project Muscular Dystrophy and the distinguished panel of advisors who contributed to this report stand ready to work alongside the FDA to strike a more appropriate balance between clinical certainty and patient access to potentially life-saving treatments. Patients and their families, frustrated by the slow pace of progress and desperate for access to new treatments for this devastating illness, deserve nothing less.

Introduction

If your child is among the one-in-3,600 male children born with Duchenne muscular dystrophy (Duchenne), the prognosis is devastating. A fatal genetic disorder, Duchenne is characterized by an inability to produce dystrophin, which is crucial for muscle function. There are no approved therapies for Duchenne. While treatment with corticosteroids can help to control symptoms and improve quality of life, it is not a cure and this disorder results in progressive and debilitating loss of function. Affected children are generally diagnosed between three and six years of age[1] and are wheelchair-bound by age 12.[2] Most will die before they reach their late twenties, generally due to weakened heart muscle, respiratory complications, or infection.[3,4]

Although Duchenne is by definition a rare disease, meaning that it affects fewer than 200,000 patients in the United States, it is the most common form of childhood muscular dystrophy. Patients and families affected by Duchenne have worked tirelessly to raise funds for research, and they have diligently sought to ensure adequate government investments in basic and clinical research and in the creation of National Institutes of Health (NIH) centers of excellence. Working in conjunction with advocates for other rare disorders, they have also appealed to Congress and the U.S. Food and Drug Administration (FDA) to ensure that the development, review, and marketing of drugs for these disorders are appropriately incentivized and tailored to address the unique challenges they present.

These efforts have helped to spur some very promising advances. The passage of the Orphan Drug Act in 1983, which grants a period of market exclusivity to treatments for rare disorders, has successfully incentivized efforts to develop new therapies for Duchenne. Just as crucially, recent advances in personalized medicine have helped to increase the number of new candidate therapies focusing on specific genetic mutations. A total of 26 compounds being investigated for the treatment of Duchenne have been granted an orphan drug designation; 18 of these within the last five years.[5] In 2010, *Muscle and Nerve* published an article authored by FDA staff in the Offices of New Drugs and Orphan Product Development, which discussed the promise of recent scientific advances and opened by stating:

> "Therapies designated to cure or reduce the morbidities associated with Duchenne muscular dystrophy (DMD) dangle before us like Tantalus' grapes."[6]

Today, there is a robust preclinical pipeline, and as many as 11 investigational compounds are in some stage of testing for the treatment of Duchenne. At least six of these compounds are now in Phase 2 or 3 clinical trials and approaching consideration for approval. Yet, it remains the case today that not a single experimental agent for treatment of Duchenne has crossed the finish line and been made commercially available to patients.

The large number of promising drugs that remain out of reach is creating enormous frustration – even desperation – for patients and their families. Although some patients are able to access these investigational compounds through clinical trials, many others are left with little hope and no treatment options due to their inability to meet inclusion criteria for trials. (Clinical trials for Duchenne frequently use a measure

A PARENT'S PERSPECTIVE: FEAR, HOPE, AND CLINICAL TRIALS

My son is a 4 year old. He was diagnosed with Duchenne in December, 2011. As any parent would imagine, Duchenne is a life-changing and devastating word for a parent to hear. My son is such a miracle to our family and friends, and he brings joy and happiness to anyone who crosses his path.

Our biggest fear is watching him get weaker, losing mobility and muscle function. Every day I dread the thought of seeing him in a wheelchair and to think of him struggling with everyday tasks. It is heart-breaking to think he will never be able to do the things that his healthy, athletic brother is able to do.

We pray every day that compounds in clinical trials are accelerated and treatments may be available that will stabilize and preserve his muscle function. There is hope in the current clinical trials and an overwhelming need for accelerated approval because of the fast progression of Duchenne.

of ambulatory ability called the six-minute walk test (6MWT) as the primary endpoint, necessarily excluding non-ambulatory patients from participation. Young children, unable to perform this test reliably are also excluded.) This has made the commercial availability of an approved treatment especially critical.

The first new drug application (NDA) for treatment of Duchenne was submitted in 2011, but the FDA refused to review the application when the data did not demonstrate statistical significance using the prospectively defined endpoint. Although retrospective analysis did show statistically significant improvement in clinical function, the FDA generally requires that analysis show an effect on a pre-determined endpoint and did not judge the retrospective analysis to be sufficient evidence of efficacy. The FDA's refusal to review the application meant that years of additional clinical testing would be needed and non-ambulatory patients would continue to be excluded from accessing the drug. By contrast, this same compound has been accepted for review for conditional approval by the European Medicines Agency. The FDA decision not to review the data has only heightened the sense of frustration and urgency among patients and families. The recent passage of the Food and Drug Administration Safety and Innovation Act (FDASIA) indicates that the Agency needs to take a more pro-active approach to the review of drugs for serious, life-threatening disorders. To review supportive data even when the a priori endpoint is not reached presents one example of how a more flexible review process would benefit all interested parties.

In the three years since the article in *Muscle and Nerve* declared that "Therapies . . . dangle before us like Tantalus' grapes," many lives have been lost to Duchenne. More young men will have lost the ability to walk, to use their hands, to breathe without difficulty. In the face of this reality, patients and their families are pressing the FDA to apply appropriate flexibility, as outlined in the relevant statute and regulations, in the review of therapies for Duchenne. Strong science and valid safety and efficacy data are of critical importance in the review and approval of any drug; the community does not want ineffective or unsafe drugs. But the evaluation of an acceptable benefit/risk ratio for treatments for serious and life-threatening disorders, such as Duchenne, must necessarily be weighed against criteria that reflect the inherent challenges in evaluating treatments for rare disorders. The criteria must also reflect the certain harm that results from a failure to treat Duchenne, which slowly robs patients of function until they die in what should be the prime of life.

Moving toward Greater Flexibility in the Review Process

FDA approval standards for all new drug applications require the demonstration of safety and "substantial evidence" of efficacy, "consisting of adequate and well-controlled investigations."[7] Safety in this context is generally defined as meaning that the benefits appear to outweigh the risks, and is considered in the context of patients without underlying health issues. Efficacy is defined as evidence of clinical benefit, and regulations in 21 CFR §314.126 paragraph (b) set out specific requirements for "adequate and well-controlled investigations." These criteria outline the acceptable types of study designs and frameworks for the review and approval of new drugs.

However, the FDA also has significant discretion at its disposal in determining whether applications have met the bar of "substantial evidence."[8] The regulations in 21 CFR §314.105(c) state that the "FDA is required to exercise its scientific judgement 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." Regulations in 21 CFR §312.80 reinforce the need for flexibility, specifically with regard to the review of drugs to treat life-threatening and severely debilitating illnesses, stating that the "FDA has determined that it is appropriate to exercise the broadest flexibility in applying the statutory standards, while preserving appropriate guarantees for safety and effectiveness." In fact, the FDA has the ability to waive any or all of the criteria outlined as required for "adequate and well-controlled investigations." The regulations in 21 CFR §314.126 paragraph (c) state, "The Director of the Center for Drug Evaluation and Research may, on the Director's own initiative or on

the petition of an interested person, waive in whole or in part any of the criteria [for "adequate and well-controlled" investigations]."

The FDA is rightly cautious in applying this discretion. In practice, new drug approvals generally require at least two well-controlled studies providing substantial evidence of safety and efficacy. On the one hand, the FDA must prevent the public from being exposed to ineffective and potentially harmful treatments. Instances of unforeseen, even fatal side-effects have reinforced this need for caution. On the other hand, the FDA must also ensure that patients have access to potentially efficacious and life-saving treatments as soon as is reasonably possible. This is a difficult balance to achieve, and there will often be unsatisfied parties on either side of a particular decision. However, there have been incremental steps to require that greater weight be given to patients' need for swift access to potentially life-saving treatments.

Advocates have long pushed for increased flexibility on the part of the FDA, particularly for serious and life-threatening illnesses with unmet medical need. The FDA itself has issued regulations outlining the appropriate application of flexibility, and Congress has responded to the demands of people living with these life-threatening illnesses by passing laws intended to speed access to new drugs, while maintaining high standards for scientific evidence. For instance, the 1997 passage of the Food and Drug Administration Modernization Act (FDAMA) codified aspects of "Subpart E" and "Subpart H" rules issued by the FDA to allow for swifter approval of new drugs in response to the AIDS crisis.[9] FDAMA created a "Fast Track" designation and allowed for the "accelerated approval of products to treat serious or life-threatening diseases based on surrogate endpoints that are reasonably likely to predict clinical benefit." It also amended the standard for substantial evidence of effectiveness to allow for "data from one adequate and well-controlled clinical investigation and confirmatory evidence (obtained prior to or after such investigation)" to serve as the basis for approval.

There has also been a move toward applying greater regulatory flexibility that is specific to the evaluation of investigational compounds for rare diseases. While the passage of the Orphan Drug Act in 1983 and FDAMA in 1997 did not establish separate statutory standards for evidence in evaluating therapies for rare disorders, the National Organization for Rare Disorders (NORD) has catalogued numerous instances in which the FDA has openly referenced the application of regulatory flexibility in response to the clinical and scientific challenges posed by rare disorders.[10] In its evaluation of 135 orphan drug approvals, NORD found that 90 were based on some application of flexibility by the FDA.[11] The FDA has rarely issued formal guidance about when and how this flexibility might be appropriately applied, however, and its application of discretion appears to differ substantially from case to case, as well as from one reviewing division to another.[12]

Opportunities in the Implementation of FDASIA

The passage of the Food and Drug Administration Safety and Innovation Act (FDASIA) in 2012 built on these earlier efforts to ensure that appropriate flexibility is applied to the review of therapies for serious and life-threatening disorders. The law includes a number of provisions aimed at speeding access to new therapies, including the creation of a break-through therapy designation, as well as a new emphasis on pediatric and rare diseases. Perhaps most promisingly, the law includes enhancements to accelerated approval intended to speed access to new therapies, and specifically references its use to approve drugs for rare disorders. The Prescription Drug User Fee Act (PDUFA) V performance goals and procedures that must be implemented under FDASIA are also of particular promise, and they commit the FDA to engaging with patient groups representing rare disorders on incorporating a structured risk-benefit assessment into regulatory decision-making. These reforms were part of a set of changes that advocates for rare disorders and other serious, life-threatening diseases had championed to address a widely perceived lack of appropriate flexibility at the FDA.

The need for these improvements has been recognized, not just by patients and their advocates, but also by industry and policy experts. The 2012

Report to the President on Propelling Innovation in Drug Discovery, Development and Evaluation issued by the President's Council of Advisors on Science and Technology (PCAST) identifies specific deficiencies in the current drug evaluation process and makes several recommendations relevant to improving the review and approval of drugs for serious, life-threatening, and rare disorders. These recommendations include the need for the FDA to expand the use of accelerated approval; expand the scope of acceptable endpoints, including surrogate and intermediate clinical endpoints; and pilot adaptive approval. PPMD endorses these recommendations, and further urges that the FDA better incorporate the perspectives of patients and care-givers into its risk-benefit assessments. This includes considering the risks of an intervention within the context of the disease under study, in this case Duchenne. As FDASIA is implemented, the FDA should seize the opportunity to speed responsible access to new therapies for serious and life-threatening illnesses where there is unmet medical need.

One of the most promising sections of FDASIA is the section addressing the use of accelerated approval, which has been enhanced to reflect advances in science. Congress included language calling for the application of this approval pathway to evaluate drugs for a broader range of disorders, including rare disorders, and the FDA must respond to these provisions as outlined below.

Recommendation 1:
The FDA should expand the use of accelerated approval for therapies intended to treat rare diseases, including Duchenne muscular dystrophy.

The changes to accelerated approval under FDASIA create a very real opportunity to improve the review of new drugs for Duchenne and other rare disorders. Section 901 of FDASIA, "Enhancement of Accelerated Patient Access to New Medical Treatments," addresses the need for the FDA's regulatory review process to evolve in order to harness scientific advances in genomics, molecular biology, and bioinformatics. The introductory language states:

> "[T]he FDA should be encouraged to implement more broadly effective processes for the expedited development and review of innovative new medicines intended to address unmet medical needs for serious or life-threatening diseases or conditions, including those for rare diseases or conditions, using a broad range of surrogate or clinical endpoints and modern scientific tools earlier in the drug development cycle when appropriate."

To help achieve this goal, Congress amended section 506 of the Public Health Service Act in order to ensure the application of the accelerated approval pathway to therapies for a wider range of disorders, including rare diseases. While the FDA has long had the authority to approve therapies for any serious or life-threating disorder with unmet medical need under accelerated approval, it has generally limited its use to a few therapeutic areas. A 2009 report by the Government Accountability Office (GAO) found that 79 out of the 90 accelerated approvals issued over the last two decades were for HIV/AIDS, cancer, or inhalation anthrax.[13] The need for FDA to apply this approval pathway to a wider range of disorders and therapeutic areas was noted by the PCAST, which recommends that the "FDA should expand the use *in practice* [emphasis added] of its existing authority for Accelerated Approval."[14]

As FDASIA is implemented, PPMD urges the FDA to ensure that the accelerated approval pathway is used to its maximum potential to evaluate therapies for Duchenne, as well as for other rare disorders. By any measure, Duchenne is a serious and life-threatening disorder with significant unmet medical need. Moreover, certain characteristics of the disease itself make the application of accelerated approval particularly crucial. The relatively small patient population affected; the variation in genetic mutations causing the disorder; the progressively debilitating nature of the disorder, where lost function may be irreversible; and the clinical variability in expression of the disease, requiring the use of different endpoints at different stages of the disease, all require the application of flexibility in the evaluation of therapies for this disorder.

Recommendation 2:
The FDA should expand the scope of acceptable endpoints, including novel surrogate and intermediate clinical endpoints, used to approve drugs for serious or life-threatening diseases with unmet medical need, such as Duchenne.

In order to help promote a broader application of the accelerated approval pathway, Section 901 of FDASIA also addresses the evidentiary standards acceptable for the justification of an approval. Specifically, under the law a product is eligible for accelerated approval:

> ". . . upon a determination that the product has an effect on a surrogate endpoint that is reasonably likely to predict clinical benefit, or on a clinical endpoint that can be measured earlier than irreversible morbidity or mortality, that is reasonably likely to predict an effect on irreversible morbidity or mortality or other clinical benefit, taking into account the severity, rarity, or prevalence of the condition and the availability or lack of alternative treatments."

The law further outlines the types of evidence that may be used to support such an approval, which:

> ". . . may include epidemiological, pathophysiological, therapeutic, pharmacologic, or other evidence developed using biomarkers, for example, or other scientific methods or tools."

In describing the purpose of these amendments, Congress made it clear that there is an expectation that these changes will speed responsible access to new therapies for life-threatening disorders like Duchenne. The PCAST report reinforces the validity of this expectation and recommends that the "FDA expand the scope of acceptable endpoints used to approve drugs for serious or life-threatening diseases with unmet medical needs." It further states, "The FDA should direct its staff, across all divisions, to make full use of the accelerated approval track for all drugs meeting the statutory standard of addressing an unmet medical need for a serious or life-threatening illness and demonstrating an effect on a clinical endpoint (other than survival or irreversible morbidity) or on a surrogate endpoint that is reasonably likely to predict clinical benefit."[15]

The imperative for the FDA to consider a wide range of evidence, including surrogate endpoints and intermediate clinical endpoints, provides an important opportunity to improve the review of treatments for Duchenne. One of the key challenges in designing and conducting trials for Duchenne has been the lack of validated endpoints, surrogate or otherwise, particularly to assess function in the non-ambulatory patient population. To date, the only endpoint that has been widely agreed upon by industry and the FDA is the six-minute walk test (6MWT). This endpoint has been validated in other disease states[16] and is a generally agreed to indicate a valid measure of clinical

A PARENT'S PERSPECTIVE: THE NEED FOR NEW ENDPOINTS

As parents of a 17 year old, our time is running out. Year after year we learn about progress but still no treatments. We understand that there must be a process, but how can that process be adapted to help the boys now?

My criteria for trials my son would or would not participate in are changing as he gets older. Duchenne has taken so much from him that I would consider treatments that would allow him to keep the function he has now, even if there are some risks. This may not have been true 10 years ago. The concept of risk vs. reward has changed for me. I think it is important to realize that in the Duchenne community there will likely be many views, but the older boys who need treatments as fast as possible are probably more willing to accept more risk for what may seem a little reward. We are willing to take a chance. It's better than no chance at all.

I think it is important for people to understand that the ability to do simple things becomes very important in daily life and contributes greatly to the boys' quality of life. Being able to brush his own teeth may not seem like much of a success, but it means so much. I think the 6 minute walk test for measuring outcomes ignores all of the possible treatments for boys who just want to preserve some dignity. To type on a keyboard at work would be a tremendously successful outcome. There has to be a way of getting treatments to these boys.

function for Duchenne patients.[17] However, reliance on this sole endpoint necessarily excludes a significant proportion of patients affected by Duchenne from participation in trials, i.e. very young patients and patients already confined to a wheelchair are unable to participate in the trial. In addition, the relatively long-time horizon over which Duchenne patients experience progressive functional decline requires lengthy clinical trials.

To help speed the evaluation of potential therapies for Duchenne, it is critically important for the FDA, researchers, and the pharmaceutical industry to work together to identify appropriate surrogate and intermediate clinical endpoints. The need for new endpoints that will allow an assessment not just of ambulatory function, but also of cardiac and respiratory function has been repeatedly acknowledged, including by staff at the FDA.[18] The PCAST, for instance, points to a suggestion by the FDA that measuring improvement in isolated muscle strength in patients with muscular dystrophy could be used as an intermediate clinical endpoint under the accelerated approval pathway.[19] Meanwhile, researchers and industry are exploring the use of biomarkers, such as imaging tests, pulmonary function tests, and dystrophin levels, as surrogate endpoints. For example, research evaluating muscle volume and intensity using magnetic resonance imaging has demonstrated value as a predictive marker of clinical function in patients Duchenne.[20] Ongoing efforts to collect and evaluate natural history data can also help bolster the evaluation of investigational therapies.

In fact, there is a strong basis for the application of surrogate and intermediate clinical endpoints to the evaluation of therapies for the treatment of Duchenne. It has been clearly established that Duchenne is caused by a genetic mutation resulting in an inability to produce dystrophin, and the pathophysiological mechanisms relating to disease progression are reasonably well understood. As a consequence, the application of accelerated approval using surrogate or intermediate endpoints would be appropriate for therapies where the mechanism of action is direct and known; where drug pharmokinetics, pharmodynamics and metabolism are relevant to the disease process being measured and can be accurately and readily measured; and where there is reliability of production and assessment of the drug.[21]

Of course, the FDA can only evaluate surrogate endpoints that are brought before the Agency; it is up to researchers and industry to define and utilize new surrogate markers in clinical trials for candidate therapies. Unfortunately, opaque evaluation metrics and a perceived reluctance on the part of the FDA to rely on new surrogate markers for the approval of drugs under the accelerated approval pathway have been pointed to as discouraging the necessary investments in research.[22] A number of reports issued by the Institute of Medicine have addressed this lack of a well-understood bar for evidence, and these reports issued recommendations for developing "well-defined consensus standards and guidelines for biomarker development, qualification, and use to reduce the uncertainty in the process of development and adoption."[23,24,25] Furthermore, published statements by staff at the FDA have at times appeared to indicate that the field has not yet achieved sufficient understanding of the pathophysiology of certain disorders, particularly for neurological disorders, that would be necessary to approve drugs based on a surrogate endpoint.[26,27]

To implement the amended accelerated approval provisions outlined in Section 901 of FDASIA, Congress directed the FDA to issue draft guidance no later than one year after the law's passage describing how these new standards for accelerated approval will be applied. It further directs that the FDA "shall also consider any unique issues associated with very rare diseases." To ensure that these provisions are implemented effectively and result in the application of accelerated approval to a broader range of disorders, PPMD urges the FDA to provide clearer and more accessible requirements on the use of surrogate and intermediate clinical endpoints. In particular, the FDA should outline the level of acceptable evidence for accelerated approval of a new drug using a novel endpoint, which presents a critically important potential pathway for providing commercial access to new therapies for Duchenne. This guidance should be consistent with the

"reasonable likelihood" standard of evidence set forth by Congress.

As the field has advanced and researchers have continued to make progress in the understanding of the pathophysiology of Duchenne and the pharmacology of the compounds under investigation, there is renewed focus on the potential to identify and utilize novel surrogate endpoints. However, some level of uncertainty will always be inherent in the use of new surrogate and intermediate clinical endpoints, and there is a compelling need to better balance the need for more evidence against the desire of patients for access to potentially life-saving treatments. Congress deliberately set the bar for evidence as "reasonably likely," and they reinforced the need to take into account "the severity, rarity, or prevalence of the condition and the availability or lack of alternative treatments." In discussing the need to increase the weight given to patient access, the PCAST recommended a renewed focus at FDA on expanding the scope of acceptable endpoints stating, "For a novel endpoint, there is no way to be certain that it will be a valid predictor of clinical benefit; errors will occur. However, for a serious disease with no good treatments, early access for patients, coupled with a requirement for ongoing knowledge-generation presents a good compromise."[28] *

Patients and the parents of patients with Duchenne are willing to trade near-certainty with regard to efficacy for a drug that is "reasonably likely" to provide clinical benefit. The alternative is the certain, debilitating progression of the disorder and near certain death by 30 years of age.

Recommendation 3:
Using existing authority under current law, the FDA should pilot the use of adaptive approval for serious and life-threatening disorders with significant unmet medical need.

In its 2012 report to the President, the PCAST recommended that the FDA should further promote access to therapies for serious and life-threatening illnesses where there is unmet medical need by piloting the use of adaptive, i.e., provisional, approval under its existing authority. PPMD endorses this recommendation and further urges the FDA to prioritize the use of adaptive approval under such a pilot program to evaluate drugs for rare disorders, including Duchenne, meeting the criteria of serious or life-threatening. As has been established, the FDA and Congress have taken steps to reinforce the need for flexibility in evaluating drugs to treat serious and life-threatening disorders, and the passage of FDASIA has further underlined the need to apply this flexibility to the evaluation of rare disorders.

The PCAST specifically recommended against new legislation to create a framework for adaptive approval, noting that the FDA has sufficient authority to conduct a pilot under its existing authority. The FDA can grant approval for drugs while requiring that post-marketing trials be conducted to provide additional evidence of efficacy and safety (see 21 CFR §312.85). While the Agency has infrequently revoked approvals on the basis of the failure of applicants receiving accelerated approval to conduct post-marketing studies,[29] it could capitalize on its ability to require post-marketing studies to facilitate a pilot of adaptive approval. This would allow for the safety and efficacy of drugs to be subjected to continuing evaluation, while providing for earlier access to potentially life-saving drugs, subject to the proviso that drugs demonstrating insufficient or negative results would have marketing approval revoked.

Given the number of promising investigational compounds under development for the treatment of Duchenne and the ongoing challenges in designing and conducting traditional clinical trials for these treatments, most notably a small, primarily pediatric patient population characterized by high clinical variability, PPMD recommends that FDA move quickly to establish a pilot program to evaluate treatments for Duchenne using adaptive approval. PPMD and the advocacy community stand ready to work with FDA and other stakeholders to undertake a process, as

*It is worth noting that the confirmatory studies required for products granted accelerated approval are designed to validate new surrogate endpoints, providing greater evidence of clinical benefit over time and helping to alleviate concerns about the relative uncertainty introduced by the accelerated approval process. If a sponsor fails to undertake post-marketing studies as required or the results indicate a lack of clinical benefit, the drug approval can be revoked by the FDA under expedited procedures.

recommended by the PCAST, to help define "potential evidentiary standards, protection of patient safety and rights, and mechanisms to ensure timely post-marketing clinical studies and withdrawal of drugs."[30]

Recommendation 4:
The FDA should give greater weight to the demonstrated benefit/risk preferences of patients, as well as caregivers in the case of pediatric illness, when making benefit/risk determinations.

Finally, the FDA performance goals outlined pursuant to FDASIA also present an opportunity to improve the patient perspective in benefit/risk assessments when evaluating treatments for Duchenne. Under FDASIA, the FDA has agreed to meet a set of performance goals in exchange for receiving the user fees paid by the pharmaceutical industry. These performance goals, known as the PDUFA V Reauthorization Performance Goals and Procedures, include a new requirement under section X for the FDA to undertake a process to enhance the patient perspective in making benefit/risk assessments. This section includes a commitment by the FDA to develop and implement a five-year plan to incorporate a structured benefit/risk assessment into the drug approval process. As a part of this effort, the Agency will undertake a public process to identify 20 disease areas where a "more systematic and expansive approach" to obtaining the patient perspective on benefit/risk assessment is needed.

With patients and their parents desperate for any new treatment that offers a glimmer of hope, PPMD recognizes that industry, advocacy groups and the Agency must act responsibly. Nonetheless, the sense of urgency is felt by all and, as a result, any discussion of benefit/risk equipoise must ethically consider the burden of disease. Furthermore, when dealing with a largely pediatric population additional challenges are posed by the very appropriate considerations in Subpart D. It is imperative to protect the right of minors, yet it is also crucial that patients are able to take advantage of new treatment options before the disease process has progressed to a stage of muscle fibrosis where treatments are less likely to be beneficial (or demonstrate a favorable response in a randomized clinical trial).

PPMD welcomes this new commitment on the part of the FDA to amplify the patient voice in drug evaluations in a structured fashion and will continue to urge the FDA to include Duchenne in the list of therapeutic areas chosen for focus. However, a five-year plan to integrate the patient perspective into the decision-making process does not adequately respond to the urgent need for new treatments for Duchenne and other life-threatening disorders. Moreover, the five-year plan outlined by the FDA will address just 20 disease areas, meaning that patients with disorders not selected could well be forced to wait much longer. The present course of Duchenne is unrelenting and irreversible. For some patients, a wait of even five years will mean the loss of the ability to walk, to breathe independently, or of finger dexterity – key for communication and independent power mobility, while others will die waiting.

Rather than proceeding slowly through a limited set of disorders, the FDA should prioritize guidance establishing new mechanisms to incorporate patient and caregiver benefit/risk preferences across all disorders and therapeutic areas. The FDA has long been charged with the need to weigh the patient perspective as part of the regulatory review process, and the Agency should immediately initiate more frequent and substantive engagement with patients and their advocates to incorporate their perspectives into the review process.

A PARENT'S PERSPECTIVE: BENEFIT/RISK IN DUCHENNE

We are living on borrowed time. My son is 15 and thankfully, still able to walk short distances. We worry about when he will stop walking and the increase in care, expense and time that will be required. We hear each tick of the clock very loudly in our heads, worried that it will take too long to develop a treatment that will slow or stop progression. I understand the need for caution and care, but I also know that my son is dying. Duchenne is terminal. Parents should be able to decide the risk/benefit of a drug that has gone through early testing. I would rather my son die trying and fighting, rather than waiting and wishing.

Summary of Recommendations

- **Recommendation 1:**
  The FDA should expand the use of accelerated approval for therapies intended to treat rare diseases, including Duchenne muscular dystrophy.
- **Recommendation 2:**
  The FDA should expand the scope of acceptable endpoints, including novel surrogate and intermediate clinical endpoints, used to approve drugs for serious or life-threatening diseases with unmet medical need, such as Duchenne.
- **Recommendation 3:**
  Using existing authority under current law, the FDA should pilot the use of adaptive approval for serious and life-threatening disorders with significant unmet medical need.
- **Recommendation 4:**
  The FDA should give greater weight to the demonstrated benefit/risk preferences of patients, as well as caregivers in the case of pediatric illness, when making benefit/risk determinations.

Conclusion

The need for strong, reliable clinical data demonstrating substantial evidence of safety and efficacy is of critical importance for the review and approval of new drugs. In weighing these data during the evaluation of new drugs, the FDA must determine in each case whether the benefits appear to outweigh the known risks. Striking the correct balance between the need for more data and access to new, potentially beneficial treatments is the constant challenge set before the Agency. To successfully navigate this challenge, it is imperative that the FDA adhere to its own guidance calling for the consideration of the relative lethality and the seriousness of the disorder the drug is designed to treat, as well as the availability or lack of alternative treatments. These considerations will vary substantially from one disorder to another, and it is often the case that patients' risk tolerance increases in relation to the morbidity and mortality associated with a particular illness.[31] To date, however, there has been little indication that the FDA is inclined to utilize the significant discretion at its disposal in reviewing drugs for Duchenne.

The passage of FDASIA and its implementation over the next several years have created new opportunities for the FDA to speed responsible access to new therapies for Duchenne and other rare, serious and life-threatening disorders. The FDA must seize this opportunity to issue guidance providing clear and accessible standards for the application of accelerated approval to therapies for Duchenne, and it should move immediately to better incorporate the patient perspective into its assessment of an appropriate benefit/risk ratio. PPMD and the distinguished panel of advisors who contributed to this report stand ready to work alongside the FDA to strike a more appropriate balance between clinical certainty and patient access to potentially life-saving treatments. Patients and their families, frustrated by the slow pace of progress and desperate for access to new treatments for this devastating illness, deserve nothing less.

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