Duchenne Muscular Dystrophy and Related Dystrophinopathies: Developing Drugs for Treatment

Guidance for Industry

DRAFT GUIDANCE

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U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

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Clinical/Medical

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Duchenne Muscular Dystrophy and Related Dystrophinopathies: Developing Drugs for Treatment Guidance for Industry[1]

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not create any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA staff responsible for this guidance as listed on the title page.

I. INTRODUCTION

The purpose of this guidance is to assist sponsors in the clinical development of drugs for the treatment of Duchenne muscular dystrophy (DMD) and related dystrophinopathies including Becker muscular dystrophy (BMD), DMD-associated dilated cardiomyopathy (DCM), and symptomatic carrier states in females.[2] Specifically, this guidance addresses FDA's current thinking regarding the clinical development program and clinical trial designs for drugs to support an indication for the treatment of one or more of these dystrophinopathies. The most prominent pathology in dystrophinopathies is degeneration of skeletal and cardiac muscle leading to progressive loss of muscle function, respiratory and cardiac failure, and premature death. This draft guidance is intended to serve as a focus for continued discussions among the Division of Neurology Products, pharmaceutical sponsors, the academic community, and the public.[3] This guidance does not address the development of drugs to treat secondary complications of muscle degeneration in dystrophinopathies (e.g., drugs specifically for heart failure or for pulmonary infections).

[1] This guidance has been prepared by the Division of Neurology Products in the Center for Drug Evaluation and Research (CDER) at the Food and Drug Administration.

[2] For the purposes of this guidance, all references to *drugs* include both human drugs and therapeutic biological products unless otherwise specified.

[3] In addition to consulting guidances, sponsors are encouraged to contact the division to discuss specific issues that arise during the development of drugs for the treatment of dystrophinopathies.

Development of this guidance was preceded by the submission to FDA of a proposed draft guidance independently prepared by a consortium of stakeholders including patients, parents and caregivers, clinicians, scientific experts, and industry representatives. The proposed draft guidance submitted by the consortium was made available through a *Federal Register* notice seeking public comment. Both the independently prepared proposed draft guidance and the public comments received in response to the *Federal Register* notice were considered in writing this guidance.[4]

This guidance does not contain discussion of the general issues of statistical analysis or clinical trial design. Those topics are addressed in the ICH guidances for industry *E9 Statistical Principles for Clinical Trials* and *E10 Choice of Control Group and Related Issues in Clinical Trials*, respectively.[5]

In general, FDA's guidance documents do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

II. BACKGROUND

Dystrophinopathies result from genetic mutations in the dystrophin gene that decrease the amount of dystrophin and/or cause dysfunction of the dystrophin protein. This dysfunction leads to muscle degeneration and, in many patients, downstream pathologies including inflammation and fibrosis that interfere with muscle regeneration and cause loss of movement, orthopedic complications, and, ultimately, respiratory and cardiac failure. The most common dystrophinopathy is DMD, with a birth prevalence of about 1 in 3,500 to 6,000 males. DMD generally has the most severe phenotype of the dystrophinopathies, with failure to reach developmental milestones, functional losses in the first decade of life, and greatly decreased life expectancy. BMD is similar to DMD but generally has later onset of symptoms and slower progression. BMD is characterized by wide interpatient variability in severity, with a clinical course resembling DMD in some patients, while others remain nearly, or in some cases completely, asymptomatic. The birth prevalence of BMD is about 1 in 20,000 males. DCM is caused by dystrophin mutations that primarily affect cardiac muscle, and is even less common. Finally, some female carriers of dystrophin mutations experience muscle degeneration similar to that in males.

[4] See 79 FR 52732, September 4, 2014.

[5] We update guidances periodically. To make sure you have the most recent version of a guidance, check the FDA Drugs guidance Web page at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm.

III. DEVELOPMENT PROGRAM

A. General Considerations

1. Early Phase Clinical Development Considerations

For a variety of reasons, communication about issues associated with both drug safety and efficacy between drug developers and those affected by dystrophinopathies is important during the development of drugs for these conditions.

- FDA recognizes that those affected by life-threatening and severely debilitating illnesses with unmet medical need are generally willing to accept greater risks and greater uncertainty about risks.[6] Nonetheless, it is important that drug developers understand from affected individuals how treatment goals and risk tolerance are related to specific patient circumstances, such as age, disease stage, and phenotype, among others. For example, tolerance for risk may differ between patients with the more severe dystrophinopathy phenotypes and those with less severe phenotypes. As development proceeds and the potential benefits and risks of a drug become more clearly understood, input from patients and caregivers should be further elicited.

- Many patients with dystrophinopathies are children. Special ethical considerations apply to the conduct of studies in children and the types and contexts of risks that are considered acceptable.[7] Within the bounds of these ethical considerations, even if risk of serious or irreversible harm is possible, drug development studies may be allowed to proceed under FDA's regulatory framework if the risks are not "unreasonable" in the context of the seriousness of the disease phenotype.[8] However, patients and caregivers can make appropriate decisions about participation in clinical trials only if provided with clear information about potential risks and benefits. In addition to informed consent based on information available at the beginning of the study, it is critical that emerging safety information be communicated rapidly to study patients and their caregivers on an ongoing basis to allow them to reassess continued participation.

- Treatment goals similarly may differ depending on patient-specific circumstances such as age and disease stage, and those patients most affected by the disease can provide insight into the outcomes that are most appropriate to designate as primary endpoints, how best these outcomes might be assessed, as well as the overall effect of a treatment on the disease.

[6] 21 CFR 312.80, subpart E

[7] 21 CFR part 50, subpart D

[8] 21 CFR 312.42

2. Drug Development Population

There is a need to understand the safety and efficacy of investigational drugs for dystrophinopathies across disease stages and phenotypes. Patients should not be unnecessarily excluded from enrollment based on characteristics such as age or disease stage unless scientifically justified. Broad inclusion criteria might also allow more rapid study enrollment, thereby accelerating drug development. Demonstrating safety and efficacy of an investigational drug generally involves several stages of development and a number of clinical trials, increasing the feasibility of including patients across different disease stages and phenotypes.

There is a strong rationale for treatment of patients at an early age because drugs that preserve muscle, in particular, may have the greatest effect on prognosis before muscle health has deteriorated. However, there is also a need to understand safety and efficacy of drugs at later stages of disease, including stages when respiratory and cardiac pathology is more pronounced.

3. Efficacy Considerations

The statutory standards for effectiveness apply to drugs for dystrophinopathies just as they do for all other drugs. FDA has long stressed, however, that it is appropriate to exercise flexibility in applying the statutory standards to drugs for serious diseases with important unmet needs, while preserving appropriate guarantees for safety and effectiveness.[9]

4. Safety Considerations

Trials in dystrophinopathies generally should be conducted under the oversight of a safety assessment committee (SAC) with access to real-time unblinded safety data. The SAC should look at frequent intervals for emerging safety signals and, if necessary, take appropriate measures to ensure that patients are not placed at unreasonable risk of harm.[10]

To support marketing approval, drug safety must be supported by an adequate number and duration of patient exposures to characterize drug risks.[11] FDA generally will consider the serious and life-threatening nature of DMD and other severe dystrophinopathies when determining the minimum number and duration of patient exposures needed.[12] Drugs shown to provide an important benefit may need less safety data to provide adequate assurance that risks are commensurate with benefits. During development, as much safety data as possible should be collected from patients across the spectrum of disease stages and severities, including, whenever possible, data from patients who may not have been included in efficacy studies but

[9] 21 CFR 312.80, subpart E, Drugs Intended to Treat Life-Threatening and Severely-Debilitating Illnesses

[10] See the guidance for clinical trial sponsors *Establishment and Operation of Clinical Trial Data Monitoring Committees*.

[11] 21 CFR 314.125(b)(2)

[12] 21 CFR 314.105(c); FDA is required to exercise its scientific judgment to determine the kind and quantity of data and information a sponsor is required to provide for a particular drug to meet the statutory standards.

in whom, based on other data, it could be possible to conclude that the drug might be effective. Safety data from a reasonable number of patients exposed to the drug for at least 1 year generally is appropriate to support approval of drugs intended for chronic use in treating DMD and other severe dystrophinopathies.

Adverse events of special interest for drugs for the treatment of dystrophinopathies include exacerbation of autoimmunity to dystrophin or other muscle components. Exacerbation of cardiac disease may be a concern for drugs that increase physiological stress on the heart by increasing the amount or activity of skeletal muscle, or for drugs that could directly affect cardiac dystrophin.

B. Specific Efficacy Trial Considerations

1. Study Design

Randomized placebo-controlled trials are strongly recommended, and generally are the most efficient way to demonstrate efficacy for drugs for dystrophinopathies. In some circumstances, however, trials using external controls, such as historically controlled trials, may be considered adequate and well-controlled, and may provide or contribute to evidence of efficacy to support approval. However, it should be noted that historically controlled trials lack important design features that reduce bias, such as randomization and masking of treatment assignment, and generally are persuasive only when drug effects are large on objective endpoints that are less susceptible to bias.[13] For externally controlled studies to be persuasive, detailed evidence should be presented that the study design and conduct adequately controlled for bias. For example, it would be critical to establish that the control group was well-matched across key baseline and prognostic variables, including age, baseline value of the primary efficacy measure and other measures of disease stage, type and intensity of supportive care, dose and duration of corticosteroid or other concomitant pharmacotherapy, and genotype, among others. Potential sources of bias, such as differences in encouragement during tests of physical performance or function, should be minimized. Again, because of the inherent limitations of externally controlled trials, treatment effects must be large to be interpretable.

Typically, drug development programs for dystrophinopathies should include early phase studies that are generally short in duration. Such studies may evaluate effects of drugs on biomarkers, to identify doses that are most likely to be effective and that are sufficiently tolerated to be studied in definitive trials of longer duration.

2. Study Population

Although there is a need to understand safety and efficacy of investigational drugs for dystrophinopathies across disease stages and phenotypes, drug development can be targeted to an identified disease subgroup when scientifically justified (e.g., drugs that are directed at specific dystrophin mutations). Similarly, enrollment can be based on early biomarker data that suggest

[13] See ICH E10.

clinical benefit is likely to occur in only a subset of patients that are identified using that biomarker.

For drugs that may reduce further clinical decline, but are not expected to improve or reverse preexisting muscle dysfunction, it may be useful to consider prognostic enrichment (i.e., the use of inclusion criteria to select patients with characteristics that predict a sufficient degree of clinical decline during the planned study). Such criteria might include a history of rapid deterioration before study entry, or more severe functional deficit at enrollment.

For drugs targeted to specific mutations, sponsors need to identify accurately the dystrophin mutation(s) of each patient for enrollment. Even for drugs intended to have mutation-independent efficacy, such testing is strongly encouraged, as knowledge of genotype-phenotype correlations may reveal differences in safety and efficacy across subgroups. For similar reasons, genotyping additional loci that modify phenotype is strongly encouraged.

For drugs in which efficacy or safety may be related to the patient's specific dystrophin mutation or to another type of finding related to a biomarker, a companion diagnostic device should be developed contemporaneously, with the clinical performance and clinical significance of the diagnostic device established using data from the clinical development program of the drug. However, given the serious and life-threatening nature of dystrophinopathies and the lack of satisfactory alternative treatments that currently exist, FDA may approve a drug even if a companion diagnostic device is not yet approved or cleared if the benefits from the use of the drug are so pronounced as to outweigh the risks from the lack of an approved or cleared in vitro companion diagnostic device.[14] This will be determined by FDA during product review.

3. Efficacy Endpoints

There is no defined set of required or recommended clinical outcome measures for studies in dystrophinopathies. Although existing outcome measures that have been developed for clinical trials and/or clinical care in dystrophinopathies or related conditions may be appropriate, FDA will also consider proposals for the use of new outcome measures that are capable of measuring clinically meaningful effects in patients. Sponsors are encouraged to propose, and, if necessary, develop, endpoints that can be used to validly and reliably assess patients with a wide spectrum of symptoms and disease stages. FDA should be engaged by a sponsor early during the selection and/or development of efficacy endpoints. Assessment of multiple efficacy endpoints should be included when feasible, to characterize the breadth of effects on dystrophin-related pathologies, including skeletal, respiratory, and cardiac muscle function, even if the study primary endpoint is only one of these measures.

Efficacy endpoints that can measure change of function over a wide range of deficits may offer a number of advantages in the development of drugs for dystrophinopathies. Such endpoints may increase the number of patients eligible for enrollment, and may decrease possible loss of information from *floor* and *ceiling* effects that occur, respectively, if a patient becomes unable to

[14] See the guidance for industry and Food and Drug Administration staff *In Vitro Companion Diagnostic Devices* (http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm081752.htm).

contribute data because he or she cannot complete a function, or remains fully capable of performing a function throughout the study time period. Endpoints that can assess function across different stages of the disease, for example, by combining measures of ambulation and upper body function, are encouraged for similar reasons. Endpoints should have the ability to detect *improvement* from baseline, as well as decline, to capture the spectrum of possible beneficial drug effects.

Patient-reported outcomes (PROs),[15] including those measuring activities of daily living, can be designed to assess the abilities and experiences of patients across a spectrum of disease stages and severities. PROs can be useful to assess the clinical meaningfulness of an objective finding of relatively small magnitude, and to contribute to assessments of benefit and risk. PRO instruments for dystrophinopathies generally should include a limited number of items that assess the most important aspects of the outcome of interest (e.g., specific aspects that contribute to health-related quality of life, such as physical functioning). PRO instruments that are too lengthy may increase responder burden and the potential for missing data. PRO instruments that are overly broad can be difficult to interpret and may be insensitive to meaningful change in the outcomes of major interest. In cases where patients are unable to report for themselves (e.g., young children), observer-reported outcomes should be based on what a caregiver or other observer directly observes during a patient's daily activities.

Efficacy endpoints based on function can be measured in a variety of ways, including performance-based outcome assessments that demonstrate the patient's ability to perform a specific activity or set of activities (e.g., ability to perform the activity(ies) (yes or no); or time required to perform the activity(ies)), or as time-to-event for decline or loss of an ability. For young children in whom abilities are still developing, it may be appropriate to assess time-to-event in the context of reaching a certain developmental milestone.

Additional considerations for endpoints include the following:

- In neonates, infants, and young children up to age 4, developmental scales have been used in DMD (e.g., the Griffiths Scale of Mental Development or the Bayley Scales of Infant and Toddler Development, Third Edition). However, the appropriateness of the use of such scales in clinical trials should be discussed and agreed upon with FDA.

- In ambulatory children from ages 4 to 7 years, the North Star Ambulatory Assessment can be a useful measure of gross motor function, as are timed function tests such as time to climb 4 stairs or time to walk or run 10 meters, among others.

- Myometry may be an appropriate endpoint for treatments that increase or preserve muscle strength, and can be reliably measured in children ages 5 years and older. The clinical meaningfulness of differences in muscle strength should be supported by the magnitude of the effect observed, or by the demonstration of a drug effect on an adequate

[15] A PRO is a measurement based on a report that comes directly from the patient (i.e., study subject) about the status of a patient's health condition without amendment or interpretation of the patient's response by a clinician or anyone else.

functional measure. In some instances, a demonstrated effect on muscle strength also can be considered as an *intermediate endpoint*, and used to support accelerated approval.[16]

- The 6-minute walk test (6MWT), or shorter versions such as the 2-minute walk test, can measure both strength and endurance, and can be appropriate for patients as young as 5 or 6 years old. A challenge of use of these tests in older patients is the floor effect of losing ambulation. The aggregated data analysis of change in 6MWT is strongly influenced by the inclusion or exclusion of patients who lose ambulation during the trial, which leads to zero values.

- For older nonambulatory patients, a number of outcome measures are available that measure primarily upper extremity function.

Many functional endpoints in dystrophinopathies can include tasks performed by a patient in a clinical setting according to instructions administered by a health care professional. Such endpoints can be affected by the effort of the patient, and/or coaching or encouragement by a family member, caregiver, or medical staff, and should be measured using procedures that minimize such bias. For example, encouragement given to patients during testing should be standardized, and whenever practicable, study personnel who are not aware of clinical course or potentially unmasking adverse events should be used to administer functional endpoints.

Efficacy in dystrophinopathies can also be demonstrated by an effect on respiratory and/or cardiac endpoints, with the following considerations:

- Specific clinical respiratory outcomes can include nocturnal desaturations, obstructive sleep apnea, aspiration pneumonia, and progression to mechanically assisted ventilation. Additional measures of respiratory function such as vital capacity, maximal inspiratory pressure, and maximal expiratory pressure, can provide additional assessment of respiratory muscle function. As with myometry, the clinical meaningfulness of differences in these additional measures should be supported by the magnitude of the effect observed, or by the demonstration of a drug effect on an adequate functional measure. In some instances, a demonstrated effect on these additional measures also can be considered as an intermediate endpoint, and used to support accelerated approval.

- Evidence of effectiveness in chronic heart failure has traditionally relied on randomized, double-blind clinical trials in adult patients with documented heart failure and/or left ventricular dysfunction caused by common etiologies such as ischemic heart disease, hypertension, or myocarditis. Most of these trials have been designed to detect outcomes such as improved survival or a composite of improved survival and decrease in heart failure hospitalizations. These trials have not used improved exercise capacity alone as an endpoint, at least in part because heart failure treatments that have improved exercise capacity have had adverse effects on survival. A treatment for DMD that was directed at

[16] See the guidance for industry *Expedited Programs for Serious Conditions — Drugs and Biologics*.

the underlying disease pathology might pose fewer such concerns, so that improved exercise capacity alone could be considered an appropriate endpoint.

- Natural history data for patients with DMD cardiomyopathy are currently limited, increasing the difficulty of developing measures that might predict disease progression or serve as surrogate endpoints. FDA recommends that, whenever feasible, sponsors collect the following cardiac data during clinical trials: periodic evaluation of signs and symptoms of cardiac involvement or heart failure that are appropriate for the age and disease stage of the study population, inventory of cardiac medications, serial electrocardiograms, and serial imaging studies (e.g., echocardiography or cardiac magnetic resonance imaging).

Dystrophin is expressed in the brain, and dystrophinopathies can be associated with cognitive and behavioral effects. Although many drugs that affect behavior would not be considered dystrophinopathy-specific (e.g., drugs for attention deficit hyperactivity disorder), drugs could be approved for dystrophinopathies if a specific beneficial effect on the nervous system were demonstrated (i.e., the benefit would not be expected to occur in patients without dystrophin mutations).

4. Study Procedures and Timing of Assessments

Drugs that will be chronically administered in dystrophinopathies should be shown to be effective for a period of at least 3 months. For drugs expected to slow functional decline, study length necessarily is affected by rate of progression in addition to predicted drug efficacy. Although studies of 1 year's duration have been conducted in DMD, the duration of studies should be based on scientifically justifiable sample size calculations that include, when appropriate, the predicted rate of functional decline in the placebo group, the anticipated effect size, the variability around these estimates, and the desired statistical power. Efficacy studies of 18 to 24 months' duration may substantially increase statistical power, while only modestly increasing overall development time.

5. Endpoint Adjudication

Blinded adjudication of cardiac endpoints has commonly been used in studies of cardiovascular drugs and should be considered if cardiac endpoints, such as heart failure or cardiac hospitalizations, are used. Adjudication should also be considered for complex respiratory endpoints, such as aspiration pneumonia, because equivocal cases may occur. Functional endpoints, such as the ability to rise from the floor or to walk, potentially may benefit from adjudication to address potential confounders such as reversible injury.

6. Statistical Considerations

In general, statistical approaches for dystrophinopathies should be similar to those used in other disease areas, as described in other guidances. Sponsors can use designs that increase the efficiency of studies (e.g., adaptive designs[17]).

For efficacy assessment based on a continuous measurement of functional capacity, statistical analyses generally should be performed on the change from baseline for each treatment group, with the treatment effect assessed by comparing the mean changes between the treatment and control groups at one or more specific times. The mean changes would normally be adjusted for the baseline measurement to improve statistical power for detecting a treatment effect.

Variability can be decreased by obtaining a baseline assessment on more than one occasion, if practicable (e.g., performing a 6MWT on two occasions, 1 week apart). For studies that require a specific degree of physical disability for enrollment (e.g., a 6MWT distance of less than 350 meters), the screening assessment used to qualify patients for study entry should not be used as the baseline assessment. A separate baseline assessment should be obtained subsequent to the screening assessment to avoid regression to the mean. For dystrophinopathies, sponsors can also consider a variation of this approach that assesses the change from baseline in the slopes (or rates of change). Whereas the typical change from baseline assessment takes only two measurements into consideration (pretreatment and post-treatment at a particular time point), assessment of slope change takes multiple measurements into consideration for each patient, thereby possibly improving statistical power to show a treatment difference.

The likelihood that randomization will be fully successful in producing comparable study arms can be increased through stratified enrollment based on one or more prognostic factors. For young children, stratification might be based on markers of lower-limb strength or ambulatory abilities, whereas for older children, pulmonary and cardiac status might be appropriate stratification factors. With small to moderate sample sizes, however, such covariates should be limited to a few that are carefully chosen.

7. Accelerated Approval (Subpart H) Considerations

In dystrophinopathies, biomarkers that reliably reflect the health and amount of skeletal muscle at a biochemical, cellular, or tissue level may be useful across the drug development process, including use as prognostic, predictive, pharmacodynamic, or, in some instances, if supported by sufficient scientific evidence and acceptable analytical methods, as surrogate endpoints to support accelerated approval. A single biomarker measure can, in different circumstances, serve different functions; for example, baseline dystrophin expression can be a marker of a patient's prognosis, whereas an increase in dystrophin could reflect biological activity of a drug, and guide key aspects of drug development such as dose selection and route of administration. Even if it cannot be concluded that a given biomarker can serve as a surrogate endpoint, positive findings based on a biomarker may help support the mechanism of action of a drug, help to identify the

[17] See the draft guidance for industry *Adaptive Design Clinical Trials for Drugs and Biologics*. When final, this guidance will represent the FDA's current thinking on this topic.

appropriate patient population to study or treat, or support the validity of findings on other endpoints. To support continued progress in overall drug development for dystrophinopathies, it is important that trials with clinically meaningful endpoints include as many biomarkers as feasible to help establish the correlation between such biomarkers and clinical endpoints.

The potential for a biomarker to predict clinical benefit in dystrophinopathies is inseparable from such factors as the magnitude of change of the biomarker and tissue in which the biomarker is measured. The meaning of a change in a biomarker might also depend on the age or disease stage of a patient, or on other patient factors such as inflammation or autoimmunity to dystrophin or other muscle components. Before studies are undertaken, sufficient analytical validity should be demonstrated, and as studies are conducted, there should be adequate assessment of the performance characteristics of the biomarker assay, including quality-control measures and documentation of results.

Deficiency of functional dystrophin appears to be the proximate cause of the symptomatic and functional consequences of dystrophinopathies, justifying particular interest in dystrophin as a biomarker, and potential surrogate endpoint for accelerated approval, and in drugs that increase functional dystrophin and/or other proteins with similar or related functions (e.g., utrophin, truncated dystrophin).

Sponsors are also encouraged to consider the use of other biomarkers, such as those measured with magnetic resonance imaging or magnetic resonance spectroscopy. Advantages of imaging include its noninvasiveness, its ability to assess large samples of muscle, the fact that it can be performed repeatedly at multiple time points, and its ability to assess multiple regions of the body, including cardiac muscle.

In some situations, accelerated approval can be based on an intermediate clinical endpoint (e.g., myometry and certain respiratory measures, discussed above). An intermediate clinical endpoint is a measurement of a therapeutic effect that can be measured earlier than an effect on irreversible morbidity or mortality (IMM) and is considered reasonably likely to predict the drug's effect on IMM or other clinical benefit. Approvals based on such intermediate clinical endpoints will be considered under the accelerated approval pathway, rather than receiving full approval, only when it is essential to determine effects on IMM or other clinical benefit to confirm the predicted clinical benefit that led to approval. Sponsors considering a development program for accelerated approval based on an intermediate clinical endpoint should discuss their development program with the Division of Neurology Products early in drug development.

8. Benefit-Risk Considerations

When making regulatory decisions regarding drugs for dystrophinopathies, FDA will consider patient and caregiver tolerance for risk, and the serious and life-threatening nature of these conditions. Patients and caregivers may be willing to tolerate substantial risk of harm if a drug might delay loss of important abilities such as ambulation. However, tolerance for risk may vary among individuals, and be affected by disease stage and severity; FDA would consider this heterogeneity in regulatory decisions.

FDA considers the totality of the available evidence when conducting a benefit-risk assessment. For example, if the effect size on a sensitive measure of muscle function is modest for a drug with substantial risks, evidence of the clinical impact of the effect provided by PROs is likely to be an important basis of benefit-risk assessments.

C. Other Considerations

1. Relevant Nonclinical Safety Considerations

Nonclinical studies provide important information upon which it can be determined whether clinical trials are reasonably safe to conduct, and to inform clinical dose selection and monitoring. For serious and life-threatening diseases for which treatments are not available or are inadequate, as a general matter, it may be appropriate to permit clinical trials to commence based on less than usual nonclinical testing if scientifically justified. In certain cases, the duration of dosing in humans may exceed that of the nonclinical studies, if justified based on the available nonclinical and clinical data. Sponsors are encouraged to consult with the Division of Neurology Products early in clinical development.

Carcinogenicity studies generally can be conducted after approval for drugs intended to treat most dystrophinopathies.

2. Pharmacokinetic/Pharmacodynamic Considerations

Given the serious and life-threatening nature of diseases such as DMD and other severe dystrophinopathies, the typical array of clinical pharmacology testing is unlikely to be needed to support a new drug's approval. For example, studies of effects of renal or hepatic impairment potentially can be deferred until after approval, or even waived, if the patient population and metabolic pathways of the drug, considered together, suggest a low likelihood of clinically meaningful effects on pharmacokinetics or pharmacodynamics. Sponsors are encouraged to consult with the Division of Neurology Products early in clinical development.

The pharmacokinetic and/or pharmacodynamic interactions between an investigational new drug and other drugs commonly used in dystrophinopathies should be defined and evaluated as needed during drug development as part of an adequate assessment of the drug's safety and effectiveness. Concomitant use of supplements, herbals, and dietary modifications is common in dystrophinopathies, and effects on the pharmacokinetics and pharmacodynamics of investigational drugs should be considered.

Sponsors should explore the relationship between exposure (drug concentration in plasma or other biological fluid) and efficacy and safety endpoints collected from clinical studies. Exposure-response relationships using biomarkers from early dose-finding studies can help identify dose/dosing regimen(s) for confirmatory studies and the need for dose adjustment for various extrinsic/intrinsic factors such as drug-drug interaction and age, among others. Importantly, these relationships can also contribute to evidence of effectiveness from confirmatory studies. The response variables used in the analyses should include prespecified

primary and secondary endpoint(s), as well as results involving biomarkers collected in the studies for efficacy and safety.

3. Labeling Considerations

Efficacy studies that enroll patients across disease stages and phenotypes are encouraged, and data from even a relatively small number of patients across different disease subgroups may help to support an indication that includes broader groups of patients. An indication narrowly restricted to the specific disease stage or phenotype enrolled in efficacy trials for dystrophinopathies is unlikely to be approved unless there is specific concern that the demonstrated effect may be limited to that particular group or that the risk is unacceptable in other groups.