Duchenne Muscular Dystrophy and Related Dystrophinopathies: Developing Drugs for Treatment

Guidance for Industry

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

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

This guidance represents the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not establish 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 office responsible for this guidance as listed on the title page.

I. INTRODUCTION

This guidance addresses FDA's current thinking regarding clinical development programs and trial designs for drugs to support an indication for the treatment of one or more dystrophinopathies: Duchenne muscular dystrophy (DMD) and related dystrophinopathies including Becker muscular dystrophy (BMD), DMD-associated dilated cardiomyopathy (DCM), and symptomatic carrier states in females.[2, 3] 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 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 pulmonary infections).

This guidance does not contain discussion of the general issues of statistical analysis or clinical trial design, as these 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.[4]

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[1] This guidance has been prepared by the Division of Neurology Products in the Center for Drug Evaluation and Research in cooperation with the Center for Biologics Evaluation and Research (CBER), 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.

[4] We update guidances periodically. To make sure you have the most recent version of a guidance, check the FDA Drugs or Biologics guidance web pages at https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm or https://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/default.htm.

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 protein and/or cause dysfunction of the protein. Protein 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 and generally most severe dystrophinopathy is DMD, with a birth prevalence of about 1 in 3,500 to 6,000 males. DMD causes delay and/or failure to reach developmental milestones, functional losses in the first decade of life, and greatly decreased life expectancy. BMD generally has later onset of symptoms and slower progression. BMD is characterized by wide interpatient variability in severity, with some patients having a clinical course similar to that observed for DMD, while other patients remain nearly, or in some cases completely, asymptomatic. The birth prevalence of BMD is about 1 in 20,000 males. DCM is less common and caused by dystrophin mutations that primarily affect cardiac muscle. Finally, some female carriers of dystrophin mutations experience muscle degeneration similar to that in males.

III. DEVELOPMENT PROGRAM

A. General Considerations

1. Early Phase Clinical Development Considerations

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

- 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 uncertainties about risks.[5] It is important that drug developers understand how affected individuals view treatment goals and risk tolerance as well the relationship between treatment goals and risk tolerance to a patient's specific circumstances. For example, tolerance for risk may differ between patients with the more severe and less severe dystrophinopathy phenotypes. As development proceeds and the potential benefits and risks of a drug become

[5] 21 CFR 312.80, subpart E.

more clearly understood, drug developers should elicit further input from patients and caregivers.

- Many patients with dystrophinopathies are children. Special considerations apply to the conduct of studies in children and the types and contexts of risks that are considered to be ethically acceptable.[6] Within the bounds of these ethical considerations, in studies where the risk to children is more than minimal, drug development studies may be allowed to proceed under FDA's regulatory framework if the risk is justified by the anticipated benefit to the child and the relation of the anticipated benefit to the risk is at least as favorable as that presented by available alternative approaches .[7] However, patients and caregivers can make appropriate decisions about participation in clinical studies only if provided with clear information about the potential risks and benefits. In addition to informed consent, and assent by children, if applicable, 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. Patients most severely affected by the disease, along with their caregivers, can provide insight into the outcomes that are most appropriate to designate as primary endpoints, how these outcomes might best be assessed, and the meaningfulness of treatment effects when considered in the context of the overall disease.

2. Drug Development Population

There is a need to understand the safety and efficacy of investigational drugs for dystrophinopathies across disease stages and phenotypes. Although drug developers may have good reasons to use prognostic enrichment to increase the likelihood of demonstrating a drug effect (e.g., to enroll patients who are more likely to experience rapid progression) or to use predictive enrichment to direct therapy to patients with a particular disease characteristic (e.g., a specific genotype or phenotype), drug developers should not unnecessarily exclude patients from enrollment based on characteristics such as age or disease stage unless scientifically justified. Broader inclusion criteria allow more rapid trial enrollment, potentially 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. There is also a need to assess safety and efficacy of drugs at later phases of disease, however, including stages when respiratory and cardiac pathology is more pronounced.

[6] 21 CFR part 50, subpart D.

[7] 21 CFR 312.42.

3. Efficacy Considerations

The statutory standards for effectiveness apply to drugs for dystrophinopathies just as the standards apply 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 unmet medical needs, while preserving appropriate guarantees for safety and effectiveness.[8]

4. Safety Considerations

Trials in dystrophinopathies generally should be conducted under the oversight of a data monitoring committee (DMC). The DMC should look for emerging safety signals at frequent intervals and, if necessary, advise the sponsor regarding appropriate measures to ensure that patients are not placed at unreasonable risk of harm.[9]

To support marketing approval, drug risks must be characterized with an adequate number of patients and an adequate duration of exposure.[10] 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.[11] Drugs shown to provide an important benefit will generally need less safety data to provide adequate assurance that benefits outweigh risks. During development, sponsors should collect safety data, including data from open-label studies or expanded access programs, from patients across the spectrum of disease stages and severities, and, whenever possible, data from patients who may not have been included in efficacy studies but in whom, based on other data, the use of the drug following approval is likely. 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 those related to immune responses 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.

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[8] 21 CFR 312.80, subpart E, Drugs Intended to Treat Life-Threatening and Severely-Debilitating Illnesses.

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

[10] 21 CFR 314.125(b)(2).

[11] 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.

B. Specific Efficacy Trial Considerations

1. Study Design

FDA strongly recommends randomized placebo-controlled trials, which generally are the most efficient way to demonstrate efficacy of drugs to treat dystrophinopathies. In some circumstances, however, FDA may consider trials using external controls (historically controlled trials) to be adequate and well controlled studies that may contribute to evidence of efficacy to support approval. However, FDA recognizes 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.[12] (Expectation bias can increase motivation in patients who know they are receiving active treatment, thereby improving patient performance on functional tests.) To support reliance on externally controlled studies, a sponsor should present detailed evidence that the study design and conduct are adequately controlled for bias. For example, it would be critical to establish that the control group was prospectively well matched to the treatment group across important 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 concomitant pharmacotherapies, and genotype, among others. Potential sources of bias, such as differences in encouragement during tests of physical performance or function, should be eliminated or minimized. The disease course in an external patient cohort can be sensitive to the date of inception and the age of patients at inception. Thus, selection of these parameters with data in hand can introduce bias. Again, because of the inherent limitations of externally controlled trials, only large treatment effects are likely to be convincing.

2. Study Population

Although there is a need to characterize the safety and efficacy of investigational drugs for dystrophinopathies across multiple disease stages and phenotypes, a sponsor can target drug development to an identified disease subgroup when scientifically justified (e.g., drugs that are directed at specific dystrophin mutations). Similarly, sponsors can base enrollment on early biomarker data that suggest clinical benefit is likely to occur in only a subset of patients that can be identified using that biomarker.

For drugs that may slow 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 more rapid 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 more information on prognostic enrichment, see the draft guidance for industry *Enrichment Strategies for Clinical Trials to Support Approval of Human Drugs and Biological Products*.[13]

[12] See ICH E10.

[13] When final, this guidance will represent the FDA's current thinking on this topic.

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, FDA strongly recommends testing because knowledge of genotype-phenotype correlations may reveal differences in safety and efficacy across subgroups. For similar reasons, FDA also strongly recommends genotyping additional loci that modify phenotype.

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 for which a suitable diagnostic device is not available, a sponsor should develop contemporaneously a companion diagnostic device. The sponsor should establish the clinical performance characteristics of the diagnostic device using data from the clinical development program of the drug. Given the serious and life-threatening nature of dystrophinopathies and the lack of satisfactory alternative treatments that currently exist, however, FDA may approve a drug even if a companion diagnostic device is not yet approved or cleared, if the benefits from the drug are so pronounced as to outweigh the risks from the lack of an approved or cleared in vitro companion diagnostic device.[14] During the drug review, FDA will determine the need for clearance or approval of the device. We encourage sponsors to engage early in development with the Division of Neurology Products or the Center for Devices and Radiological Health at FDA to discuss the potential need for the codevelopment of a companion diagnostic device

3. Efficacy Endpoints

FDA has no defined set of required or recommended clinical outcome measures for studies in dystrophinopathies. Although existing outcome measures 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 novel outcome measures that are capable of measuring clinically meaningful effects in patients. FDA encourages sponsors to propose and, if necessary, develop endpoints that can validly and reliably assess patients with a wide spectrum of symptoms and disease stages. Sponsors should engage FDA early during the selection and/or development of efficacy endpoints. The sponsor should include an assessment of multiple efficacy endpoints, when feasible, to characterize the breadth of effects on dystrophin-related pathologies, including skeletal, respiratory, and cardiac muscle function, even if the primary endpoint is only one of these measures.

Efficacy endpoints that can measure change of function over a wide range of types and severity 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, when patients become unable to contribute data because they can no longer complete a function, or remain capable of performing a function throughout the study. For similar reasons, FDA encourages sponsors to use endpoints that can assess function across different stages of the disease (e.g., by

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

combining measures of ambulation and upper body function). 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 overly lengthy may increase responder burden and fatigue, increasing 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 a patient is unable to report for himself or herself (e.g., a young child), the sponsor should base observer-reported outcomes on what a caregiver or other observer directly sees during a patient's daily activities.

Sponsors can measure efficacy endpoints based on function 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); 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 positive sense (i.e., the time to reach a certain developmental milestone).

Additional considerations for endpoints include the following:

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

- In ambulatory children ages 3 years and older, the North Star Ambulatory Assessment or an age-appropriate modified North Star Ambulatory Assessment can provide a useful measure of gross motor function, as can timed function tests such as time to climb four 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 it can be used to provide reliable measurements 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 appropriate functional measure. In some instances, a demonstrated effect on

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

muscle strength could be considered an *intermediate clinical endpoint* and be 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 of age. There are challenges associated with the use of these tests. First, performance tends to improve with time in very young patients whereas performance tends to worsen with time in older patients. Second, there can be a floor effect of losing ambulation in older patients with more advanced disease. Analyses of change in 6MWT can be strongly influenced by the inclusion or exclusion of patients who lose ambulation during the trial; such patients contribute zero values. Third, considering the above, the data may not be normally distributed, which can have important analytical ramifications.

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

Many functional endpoints in clinical trials for dystrophinopathies 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 so that blinding to treatment is critical. Sponsors should consider other ways to minimize such influences. For example, sponsors should standardize the encouragement given to patients during testing, and whenever practicable, study personnel who are not aware of clinical course or potentially unmasking adverse events should administer tests of 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 desaturation, 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 also be used. As with myometry, sponsors should support the clinical meaningfulness of differences in these additional measures by examining the magnitude of the effect observed (both mean effect and distribution of responses) or by the demonstration of a drug effect on an adequate functional measure. In some instances, a demonstrated effect on these measures could be considered an intermediate clinical 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

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

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 directed at the underlying disease pathology might pose fewer such concerns so that FDA could consider improved exercise capacity alone to be an appropriate endpoint. One obvious disadvantage of an approach demonstrating improvement in exercise capacity is that the effects of skeletal muscle function and cardiac muscle function might not be easily distinguished.

- Few natural history studies exist for patients with DMD cardiomyopathy, which increases the difficulty of developing measures that might predict disease progression or serve as endpoints for accelerated approval. 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 trial population, inventory of cardiac medications, serial electrocardiograms, and serial noninvasive 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), FDA could approve a drug 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 to patients with 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 the rate of progression in addition to predicted drug efficacy. Although studies of 1 year's duration have been conducted in DMD, sponsors should base the duration of studies 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 sponsors should consider this if cardiac endpoints (e.g., heart failure, cardiac hospitalizations) are used. Sponsors should also consider adjudication for complex respiratory endpoints (e.g., aspiration pneumonia) because equivocal cases may occur. Functional endpoints (e.g., the ability to rise from the floor, to walk) potentially may benefit from adjudication to address potential confounding factors 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, sponsors generally should perform statistical analyses 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.

Overall, a study should be adequately powered to be able to detect a treatment effect in the study population taking into account the estimated effect size. Because of the limited number of patients with DMD, however, it may not be realistic or feasible to adequately power the study to attain statistically significant results for each distinct subpopulation of interest in the study. If the sponsor has obtained statistically significant results demonstrating efficacy in the overall target population, favorable trends in the efficacy results may support the inclusion of a description of subpopulations within the clinical trials section of labeling.

Sponsors can decrease variability 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 sponsor should obtain a separate baseline assessment after the screening assessment to limit 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 posttreatment 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 randomization 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, sponsors should limit such covariates to a few that are carefully chosen.

7. Accelerated Approval 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,

[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.

including use as prognostic, predictive, or pharmacodynamic markers, 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 identify the 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, trials with clinically meaningful endpoints should include a selection of relevant biomarkers to help establish the correlation between such biomarkers and clinical endpoints.

The potential for a biomarker to predict clinical benefit in dystrophinopathies could relate to 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. When biomarkers are assessed, analytical validity should be demonstrated to the extent possible, and 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 as a potential surrogate endpoint for accelerated approval.

FDA also encourages sponsors 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.

Sponsors considering a development program intended to support accelerated approval should discuss their development programs 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. For example, patients 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.

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 human studies 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.

Studies in juvenile animals, to assess the potential for toxicity to immature systems and developmental processes, should be conducted to support clinical studies in the pediatric population. The design of studies in juvenile animals[18] and timing of submission during clinical development should be discussed with the Division prior to study initiation. 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, FDA can defer until after approval, or waive, studies of effects of renal or hepatic impairment if the patient population and metabolic pathways of the drug, considered together, suggest a low likelihood of clinically meaningful effects on pharmacokinetics or pharmacodynamics. FDA encourages sponsors to consult with the Division of Neurology Products early in clinical development.

Sponsors should define and evaluate as needed the pharmacokinetic and/or pharmacodynamic interactions between an investigational new drug and other drugs commonly used in dystrophinopathies 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 sponsors should consider the potential effects of these on the pharmacokinetics and pharmacodynamics of investigational drugs.

Sponsors should explore the relationship between exposure (drug concentration in plasma or other biological fluid) and efficacy and safety endpoints. 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 interactions, age, and renal function, among others. Importantly, exposure-response assessment can also contribute to evidence of effectiveness from confirmatory studies. The

[18] Such studies may not be needed for gene or cell therapy products regulated by CBER. Sponsors should consult with CBER early in clinical development to discuss the need for juvenile animal toxicology studies.

response variables used in the analyses should include prespecified primary and secondary endpoints, as well as results involving biomarkers collected in the studies for efficacy and safety.

3. Labeling Considerations

FDA encourages sponsors to enroll patients across disease stages and phenotypes. 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. In general, FDA will consider approval for a broader patient population unless issues (e.g., an unacceptable safety risk, an expected lack of effectiveness in certain subpopulations) exist that provide arguments against such an approach.