Chapter 11
Key Challenges to the Approval of Products to Treat Patients with Muscular Dystrophy

Raymond A. Huml

Introduction

Although the first product for muscular dystrophy (MD) has been tentatively approved in Europe (for DMD), significant hurdles—including the identification of patients for clinical trials and the need to better understand the natural history of disease progression—remain to gaining regulatory approval of products to treat all patients with MD. Unfortunately, no MD products have yet been approved in the U.S.

The most progress has been made in DMD/BMD and the promulgation of regulatory guidance started in the EU in 2011. Regulatory advice is available in the EU for sponsors and investors in DMD/BMD clinical trials, which may help sponsors of products to treat other types of MD in the U.S. The U.S. is currently relying on programs already in place to advance products for rare diseases, including MD, and, in an unprecedented move, the FDA encouraged a patient advocacy group to submit draft guidance to help guide sponsors of MD products and decrease the risks associated with MD drug development.

Despite the challenges, substantial progress has been made and there are a number of late stage candidates in clinical development primarily for DMD (see Chapter 12 for a discussion of pharmaceutical products as potential treatments for patient with MD). Much more work is desperately needed to address the other eight types of MD.

Many people are not aware that MD is actually a group of diseases with different clinical manifestations and marked variance in progression, even within families and between siblings. The author has met multiple physicians and residents who have never seen a patient with FSHD or have only ever seen one or just a few patients with some type of MD. In addition, most of the types of MDs (e.g., oculopharyngeal MD

R.A. Huml, M.S., D.V.M., R.A.C. (✉)
Biosimilars Center of Excellence, Quintiles Inc., 4820 Emperor Boulevard, Durham, NC 27703, USA
e-mail: raymond.huml@quintiles.com

R.A. Huml (ed.), *Muscular Dystrophy*, DOI 10.1007/978-3-319-17362-7_11

and facioscapulohumeral MD) have very difficult names to pronounce and generally require an explanation to other family members, as well as healthcare providers (e.g., physician assistants), diagnostic technicians (e.g., x-ray technicians), and caregivers.

This lack of education and clinical awareness makes it difficult to discuss, much less manage, some of the risks associated with the clinical development and the capital required to develop products for the treatment of MD. This book is one small step towards narrowing this awareness gap.

The key challenges associated with the approval of products to treat patients with MD revolve around the science, which translates into therapeutic targets, and later to animal models of disease, and then to clinical trials in humans.

Natural history studies are required to understand the progression of the disease in groups or individuals with the disease. Once a long time-frame has been studied (e.g., >20 years), one can get an idea of the progression seen in a group of patients with a particular type of MD. Scientists who deem it unethical to study patients with MD using a placebo comparator arm (in case the drug is effective) may wish to study an investigational drug vs. the natural history progression to understand if disease progress is delayed or halted (by a disease-modifying therapy) or even better, reversed (a cure). Natural history studies are slowly being accomplished for MD types such as DMD and BMD, but less so for other types of MD. See Chapter 12 for additional details.

As the properties of an investigational drug become better known—usually through laboratory and animal experiments (during the preclinical phase of drug development)—scientists can develop and test theories to see if they can alter (upregulate, downregulate, or block) a biochemical pathway that might influence the disease in humans.

This chapter will begin with a discussion of two recently approved FDA documents (see Table 11.1), which provide the greatest amount of insight into MD drug development in the U.S., and end with a discussion of other considerations not included in the two regulatory documents. Interested readers (patients, caregivers, investors, drug developers) are encouraged to read both FDA documents in their entirety. One document, focused on rare diseases, was produced as a requirement of the FDA Safety and Innovation Act (Section 510 and PDUFA Performance Goals

Table 11.1 Key FDA documents providing insights into MD clinical drug development in the U.S.

Name of document	Date released
Report: *complex issues in developing drugs and biological products for rare diseases and accelerating the development of therapies for pediatric rare diseases including strategic plan*: *accelerating the development of therapies for pediatric rare diseases*	July 2014
Guidance for Industry, *Duchenne muscular dystrophy*, *developing drugs for the treatment over the spectrum of disease* prepared and submitted by Parent Project Muscular Dystrophy (PPMD) to the FDA	June 25, 2014

Section IX.E.4) and is not specific to MD drug development; the other document is specific for MD, but is limited to DMD drug development.

There are a number of key hurdles common to the approval of all potential products to treat MD, either as a rare disease or as a form of MD, that can benefit from the advancement in DMD/BMD clinical drug development. To facilitate discussion of these hurdles, the first document, highlighting rare diseases, will be discussed, followed by a discussion of the Parent Project Muscular Dystrophy (PPMD) document, highlighting challenges that may have a wider applicability to non-DMD types of MD.

FDA's report and strategic plan on the complex issues in developing drugs and biological products for rare diseases is a useful backdrop for insights into this complex problem. The report is the result of efforts that started in 2012 when the U.S. Congress passed the FDA *Safety and Innovation Act*, which mandated holding a public meeting to encourage and accelerate the development of new therapies for pediatric rare disease as well as issuing a report that includes a strategic plan to address such therapies. The FDA held that meeting on January 6–8, 2014, for the Agency to solicit input from various stakeholders. The important issues that were discussed at the meeting included:

- The need for more comprehensive information about the natural history of most rare diseases.
- The importance of public–private, public–public (interagency and intergovernmental), and international partnerships in providing resources and facilitating data collection.
- Recommendations for greater involvement and a more active role for patients and caregivers in therapeutic product development.
- The invaluable contribution of advocacy groups in the development process to educate and recruit patients, and to assist in endpoint selection.
- The concept that patients' and families' willingness to accept risk for participation in clinical trials, and for adopting new therapies, may be greater for those affected by serious and life-threatening rare diseases.
- Methods to overcome the challenges of trial design, such as flexible drug development programs, adaptive trial designs, enrichment strategies, and master protocols.
- Endpoint development and acceptance for use in registration trials (e.g., patient reported outcomes and surrogates).
- The ways in which benefit–risk assessments guide regulatory decision making.

Several important issues were raised that fell outside of the FDA's jurisdiction, including issues dealing with reimbursement and the governance and management of patient registries. The reimbursement topic, while critically important to families with MD, is beyond the scope of this chapter. Patient registries are further discussed in Chapter 14.

Highlights of the FDA Report [1], as pertinent to MD, are provided below. Key hurdles and challenges are highlighted in *italics*.

Clinical Trial Design Issues

According to the report, and many researchers, to effectively study drugs that can be used to treat a disease, researchers must fully understand the disease's natural history, the term used to describe how a disease would evolve if no treatment were given.

At present, the natural history of all nine types of MD is not fully known. Given the wide variation between the various types of MD, this issue is problematic.

The organization of natural history studies and disease registries is needed.

At present, these studies and registries are not standardized, transparent, nor compatible regarding data collection among multiple database holders.

There is no consensus on how to determine endpoints for clinical trials that are clinically meaningful to patients with rare diseases.

It was suggested at the FDA meeting that patient advocacy groups could be hubs for data collection and could help facilitate development of patient-reported outcomes for patients with specific diseases. Other sources could include published case studies, cross-sectional analyses, and prospective longitudinal natural history studies with information on phenotypic and genotypic characteristics of the disease, available biomarkers, and clinical manifestations.

According the FDA report, ***the greatest challenge in designing and interpreting clinical trials in rare diseases is the small numbers of patients available for clinical studies***. Such small numbers of patients, if studied using conventional study design, are often unable to generate enough data to establish the efficacy and safety of the drug. Compounding this challenge is the fact that the few patients who are available for the study may exhibit varying signs of the disease or react to medications intended to treat their condition in different ways. New methods to address these challenges include various crossover designs, and use of historical control studies and enrichment strategies.

The Benefit–Risk Assessment

It was acknowledged that patients, physicians, and regulators are willing to accept greater risks when dealing with serious diseases, and that the FDA promotes transparency in informing patients through informed consent and appropriate product labeling once the product is approved.

Risk tolerance would be expected to change as more treatments became available for a particular condition.

Parents from both the panel and the audience agreed that delaying disease progression in order to give their child a more fulfilling childhood experience would be beneficial. The uncertainty of the level of risk of an experimental intervention in order to delay disease progression was contrasted with the certainty of progressive deterioration and death due to the disease in certain forms of MD.

An important decision that is made when developing products for the treatment of rare pediatric diseases is whether there are sufficient data to support giving an experimental product to a child. This decision becomes more critical in first-in-human testing of a product for rare and life-threatening diseases with no known treatments. The panelists focused on three concepts that help to inform this decision: (1) the desired clinical benefit; (2) the probability and nature of the harms (i.e., risks) that may be acceptable to attain those benefits; and (3) the amount of uncertainty about each that is tolerable.

The panelists agreed that when considering whether the risks of an experimental product are either "reasonable" or "justified," both the type of harm that the product might cause, and likelihood that the harm may occur should be considered. *There was consensus that patients' and families' attitudes about benefit–risk should be solicited as part of the process, but it was acknowledged that these attitudes may change over time, with disease progression*. Patient advocates noted that stabilization may be seen as a reasonable benefit, as opposed to the ideal of a cure, and that even the risks for certain harms may be acceptable given the potential for slowed progression of the disease.

Long-Term Safety Concerns

Because *clinical trials for rare disease therapies are often too small to definitively ascertain a drug's complete safety profile*, for example, failing to reveal uncommon adverse events (AEs), it is important to perform long-term safety assessments (e.g., pharmacovigilance).

Patient Registries

A patient registry is a list or database of patient information that scientists and researchers can use to keep track of patients who have participated in clinical trials, including all relevant study information, to monitor potential long-term health effects of a given therapy and shape future clinical trials.

The report discussed the value of patient registries in moving clinical research forward. Patient registries can: (1) improve patient recruitment; (2) identify possible patient cohorts for study; (3) serve as a lead-in to natural history studies; (4) integrate patient reported and clinical data from multiple sources into a single repository; (5) stimulate new research and lead to new scientific insights; and (6) enhance creative data mining within and across disorders. When developing a new registry, the following should be taken into consideration: (1) the purpose of the registry; (2) the process of data (identified and de-identified) collection, management, and analyses across multiple platforms; (3) the data curator's role; (4) the type of informed consent needed (restricted or broad access); (5) Institutional Review Board and

Federal Information Security Management Act requirements; (6) data sources (patient, family, care-giver, and healthcare provider); (7) uses of common and unique data elements; and (8) options for data updates. *It is important to further develop partnerships and collaborations between stakeholders in the rare disease community*, and to agree upon the use of common and unique data elements in order to contribute to the sharing of data.

In the context of addressing clinical trial hurdles, patient registries are another tool used to monitor outcomes in patients after the trial is complete. Patient registries allow for long-term follow-up of patients and can foster relationships among patients with rare diseases, their caregivers, healthcare providers, and drug developers. For additional information on patient registries, see Chapter 14.

Dose Selection

Other clinical trial challenges include determining the adequate drug exposure (what doses to study and what duration of exposure to assess) and the appropriate size for a safety database.

The report suggested, with regard to dose selection, that clinical trials should assess the safety of a range of doses, rather than focusing on a single dose. Suggestions, by panelists interviewed in the report, were made for ways to explore the safety of doses (e.g., adaptive dose finding, and use of biomarkers in dose finding and dose response).

Gene Therapy

The spectrum of diseases for which gene transfers or therapies (hereafter referred to as gene therapies) may be used is wide-ranging. Since children potentially have many years of life ahead of them, *the issue of possible long-term permanent effects of gene therapy is critical*. These issues include the need to address long-term safety risks for children and the requirement for long-term safety follow-up. This session focused on a discussion of the development of products with uncertainty regarding their long-term benefits and risks.

Gene therapy may provide the prospect of a cure or substantial amelioration of a condition after a single administration of the product. *Patients may also incur gene-therapy-related harms*, *which may be prolonged or which may appear only after a long interval following treatment. For this reason*, *long-term follow-up is critical for gene therapy trials*. The decision to participate in trials requiring long-term safety follow-up is based on the natural history of the disease, the stage of disease, and whether long-term follow-up is prohibitive. This decision is also dependent upon whether other treatment options exist.

Statistical Considerations

Bayesian methods combine prior information, such as that gathered in previous trials on a related product or the same product on a different population, with current trial data on an endpoint of interest (e.g., an adverse event rate), in order to form conclusions about the endpoint. Bayesian statistical methods can be used to make inferences about rare diseases in pediatric populations. *Challenging issues with studying rare diseases in pediatric populations include dealing with small sample sizes and estimation of the occurrence of rare events*. Bayesian methods can be used to overcome these issues. They provide a way to learn from evidence as it accumulates.

A full discussion of biostatistics is beyond the scope of this book; however, additional details can be found in FDA's final guidance document on Bayesian statistics titled, Guidance for the Use of Bayesian Statistics in Medical Device Clinical Trials.

Lack of U.S. Regulatory Precedence

Common issues in drug development for rare diseases include the *small numbers of patients with the individual disease available for study*, *phenotypic heterogeneity*, *and often*, *a lack of regulatory precedence. The lack of regulatory precedence often means there is a lack of accepted endpoints*, *outcome assessment measures*, *instruments*, *and tools for the study of the disease*.

FDA plans to issue guidance to facilitate understanding of these common rare disease issues. Although *there is no deliverable specific to pediatrics or MD associated with this document*, some of the common issues in rare disease drug development, such as the small numbers of patients available for study, are compounded when developing drugs for children. Therefore, FDA advice on managing these common issues should be helpful to developers of therapies for pediatric rare diseases.

Call for Additional Patient Participation

Patient participation in the process of drug development is important because they can provide the unique perspective on their disease, its effect on daily life, and the tolerability of currently available therapies. Through an understanding of the patients' and their caregivers' perspectives, developers can ensure that potential treatment effects on aspects of daily life that are important to patients are adequately captured in clinical trials. Further, this information can be helpful to FDA's review of applications for new drugs, particularly when the impact of a disease on patients is not well understood or endpoints for studying drugs for a disease are not clearly defined or established.

The *Patient-Focused Drug Development Program* provides a mechanism for obtaining patients' and caregivers input on specific disease areas, and FDA has committed to examining 20 disease areas over five years. Considerations in the selection process included disease areas:

- That are chronic, symptomatic, or affect functioning and activities of daily living
- For which aspects of the disease are not formally captured in clinical trials
- For which there are currently no therapies or very few therapies, or the available therapies do not directly affect how a patient feels or functions.

For each disease area selected, the agency is conducting a public meeting to discuss the disease and its effect on patients' daily lives, the types of treatment benefits that matter most to patients, and patients' and caregivers' perspectives on the adequacy of available therapies. These meetings include participation of FDA review divisions, the relevant patient community, and other interested stakeholders.

PPMD Report

Additional insights into the complexities and hurdles to successfully conduct MD research can be gleaned from the PPMD-initiated FDA Guidance Document [2] on DMD/BMD, published July 2014, with key excerpts and thoughts summarized below.

Lack of Specific MD Regulatory Guidance

The first hurdle, identified on Page 2 of the PPMD report, is that—with the exception of their own guidance (which is subject to change, may or may not be approved by the FDA, and is focused only on DMD/BMD)—the *U.S. lacks specific guidance for the clinical development of treatments for any other type of MD*.

In response to a lack of specific guidance in the U.S., the PPMD guidance discusses three regulatory pathways for expedited approval, in addition to traditional drug approval.

Please note that *these regulatory pathways are not unique to MD* and they are already established:

1. Priority review
2. Accelerated approval
3. Breakthrough or fast track

It should be noted that, like other U.S. guidance documents (and contrary to EU regulatory guidance, which does hold legal force), the *DMD guidance does not establish legally enforceable responsibilities*.

Although probably the best understood of the MDs, the natural history of DMD/BMD is not 100% understood or fully charted, despite many years of funding by government and advocacy groups, such as the Muscular Dystrophy Association (MDA). Given the *paucity of natural history understanding for some of the other types of MDs*, it has been discovered that the course of disease for DMD can be significantly altered by therapies such as long-term glucocorticoids and the management of spinal deformity. Additional details regarding regulatory guidance are provided in Chapter 10.

The Benefit–Risk Assessment

The DMD guidance generally supports the rare disease discussion regarding the risk/benefit assessment, in that parents of the DMD population are willing to accept more uncertainty and take greater risk early on, because of the predictable and severe outcomes of the disease. Importantly, for patients with other types of MDs, the guidance recommends that the FDA better incorporate the perspective of patients and families into the benefit–risk assessment.

Unlike traditional clinical trial development, sponsors were advised to quantify the preferences of patients and family members, when feasible.

For DMD, *caregivers were willing to accept a serious risk when balanced with a non-curative treatment*, *even absent lifespan improvement*. In essence, stabilization of the child's progression was considered a benefit worth a serious risk; however, caregivers indicated a limit to their risk tolerance in that they would not accept a risk of death and a risk of additional lifelong disability for a drug that stopped or slowed progression.

Delay to Diagnosis

DMD is like other types of MD in that there can be a significant delay to diagnosis. Despite early signs of weakness, parents may not voice their concerns or local healthcare professionals not familiar with MD may delay in pursuing testing. The delay can be substantial—as long as 2.5 years according to a MD-STARnet report and other sources [3, 4]. It has also been reported that teachers may notice clinical signs and development delays that were not recognized by health professionals. This lack of awareness suggests that the education of practitioners is critical to shortening the diagnostic odyssey (See the American Academy of Pediatrics statement on www.childmuscleweakness.org).

Differences in Diagnostic Testing

Not all types of MD can be diagnosed with accuracy and some subtypes of certain types of MD may not yet be identified.

Further complicating matters is the *difficulty due to heterogeneity in multiple types of MDs*. For clinical trial participation, and in the author's experience of reviewing the literature, a molecular diagnosis is preferred over a clinical diagnosis. This helps to decrease the variation within the patient population and increase the probability of success for targeted therapies; however, even with DMD, as many as ~5% of mutations are undetectable by standard genomic analysis [5, 6].

Because our understanding of genetics is evolving, *patients who have been screened by older techniques may need to be re-tested in order to more accurately diagnosis their mutations*. Barriers to obtaining the latest genetic testing include: reluctance to visit caregiver, financial (cost), reluctance to give blood or other tissue sample, and inadequate healthcare provider education. It has been noted that because of the potential for early intervention, newborn genotypic screening is recommended, but has not yet been fully worked out. Barriers for early diagnosis include reluctance of health insurers to pay for this service due to increased cost, need for informed consent and accuracy and interpretation of the tests, meaning that genotype alone does not determine classification of all patients and cannot replace the clinical assessment.

Natural History

As mentioned earlier, although significant advances have been made, *the natural history is not understood for all types or subtypes of the nine forms of MD*. Further work is needed to elucidate these time courses. As the PPMD paper points out, significant work was done for DMD to enhance the understanding of DMD natural history from additional data from registries and the placebo arms of industry trials. These approaches could be used for other types of MD, especially in light of the paucity of patients that can be identified and are willing to enroll in clinical trials.

Testing and Evaluation of Clinical Endpoints with Validation

Additional work is needed to identify clinically validated endpoints for clinical trials; however, significant progress has been made for DMD that may apply to other types of MD. For example, Timed Function tests, such as the six-minute walk test (aka 6MWT—one of the most commonly used primary outcome measures in clinical development programs), can be used to assess progression of MD. Stair climbing, and strength tests, including manual muscle testing, quantitative lower and

upper limb testing, and some patient reported outcomes, may have applicability for other types of MD in the clinical trial setting.

It should be noted that *concurrent medical management may alter the course of MD disease* and this has certainly been the case for DMD where glucocorticoids and other interventions have altered (improved) the natural course of the MD and these factors need to be accounted for in clinical trial drug development. For example, a Cochrane review concluded that for DMD, glucocorticoid corticosteroids improve muscle strength and function over six months to two years.

The loss of clinical milestones is a hallmark of disease progression in DMD, but may be true for other types of MD as well. For example, a number of ambulatory functions and milestones are listed and include:

- Unable to jump, hop, and run
- Loss of standing from the floor
- Loss of transition from lying supine to sitting
- Loss of stair climbing
- Loss of ability to stand from a chair
- Loss of ability to walk independently (defined by the inability to perform a 10 m walk/run)
- Loss of standing in place

And non-ambulatory milestones:

- Loss of ability to reach overhead
- Loss of ability to reach the scalp
- Loss of ability to self-feed without adaptations (hand to mouth)
- Loss of ability to place hands to table top
- Loss of ability to use a computer (distal hand function)

Although the focus of most research is on the ambulatory MD patient population, outcome measures will also need to be validated for patients in the non-ambulant population and multiple scales are discussed in the PPMD document that may apply to other types of MD as well.

Heterogeneity

As noted elsewhere, the goal of therapeutics in MD is to slow or stabilize disease progression in comparison to that expected from natural history. Heterogeneity among patients means that some patients with MD may experience more aggressive forms of progression than others. These subtleties need to be addressed in clinical trials and can include:

- Future progression due to disease severity, stage of disease, and known natural history
- The age at loss of clinically meaningful milestones as a surrogate for disease severity

- Imbalance of the ages of study participants
- Imbalances in gender (not discussed in the PPMD paper, but important nonetheless)
- Genetic predictors of disease progression (mutations)
- Genetic modifiers (based on genetic screening that may identify genetic polymorphisms in other genes as well)
- Previous treatments (e.g., glucocorticoids)
- Previous adaptive treatments (splinting, orthotic devices, corsets, etc.)
- Physical therapy (length, type, and progress).

Other Obstacles

In addition to the hurdles identified in FDA's rare disease and PPMD documents, other factors have hampered MD drug development. For example, animal models of MD do not accurately reflect human disease; thus, the majority of drugs tried in animal models have failed in human clinical trials [7, 8]. As a result, increased rigor and higher standards are needed in the preclinical space. Current data suggest a tendency to move to MD clinical trials too soon and based on insufficient data [9, 10].

Other hurdles not already discussed include:

- Difficulty in defining and measuring the rate of change in slowly progressing disease conditions.
- Variety and differences in the genetic mode of transmission over the nine types of MD (e.g., autosomal dominant inheritance, autosomal recessive inheritance, germline mosaic [resulting from a mutation during development that is propagated to only a subset of the adult cells, such as sperm or eggs], de novo mutations, etc.).
- Heterogeneity of the phenotypes within each form of MD with varying treatment goals at each stage.
- Few patients being available or eligible for study in clinical trials. Although already stated, on the positive side—for example, for drug developers—it should be noted that because of the paucity of patients eligible for clinical trials, that the FDA is willing to classify MD candidates as orphan drugs. As orphans, they would garner significant advantages for the sponsor, such as regulatory exclusivity and reduced fees during the application process.
- Pediatric neuromuscular disease presents a challenge because patients lose muscle function as they grow into adolescence. Therapies, if not definitively curative, must provide a benefit–risk ratio acceptable to patients as well as caregivers; these two parties may not calculate the benefit–risk ratio in the same way.

For additional details, see Chapter 6 titled, "Transition from Childhood to Adult in Patients with Muscular Dystrophy" by Drs. Kathryn Wagner and Elba Y. Gerena Maldonado.

Summary

A major challenge in developing therapies for DMD is that there is considerable variation in the severity and rate of disease progression in different individuals. Other hurdles include: difficulty in defining and measuring the rate of change in this slowly progressing disease; variation in the goals of treatment at each stage of DMD; and the fact that few patients are available or eligible for study in clinical trials.

Driven by the desperate need for a cure, governments and U.S. patient advocacy groups for patients with DMD (and its cousin, BMD) have led the way for patients with other types of MD, providing a surrogate pathway for other patient advocacy groups.

Europe is focusing on providing more detailed regulatory guidance, in line with its historical guidance for drug developers, but, while encouraging, this is limited. For example, in its only MD guidance, the primary focus is on male children with DMD and does not fully address parameters for women, men, and female children. The guideline also includes only a few references to BMD patients.

The U.S. is relying on current programs already in place and needed to solicit help from patient advocacy groups, such as the PPMD, in order to provide regulatory guidance. The current lack of detailed regulatory guidance adds risk to sponsors' drug development programs. Justifiably starting with DMD, the most severe form of MD, additional regulatory guidance along the lines of that provided by PPMD is desperately needed to de-risk the programs of sponsors developing treatments for the other forms of MD, such as FSHD.

Once drug developers identify enough patients to study, but before moving to clinical trials, they need to have a minimum understanding of the natural history for each type of MD and make sure that the preclinical data package justifies the risk/benefit to the patient (and caregivers).

Other hurdles to product approval for MD include the lack of protein identification and complete understanding of the mechanism of action in certain types of MD (e.g., FSHD), and lack of regulatory agreement on primary and secondary endpoints in the U.S. For example, scientific debate continues on whether Sarepta Therapeutics can use dystrophin as a surrogate endpoint for registration purposes.

Until clinical endpoints and other key clinical trial design features are provided in U.S. and EU regulatory guidance, sponsors of drugs will need to collaborate with regulatory agencies on a case-by-case basis and early solicitation is encouraged.

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