TO: Janet Woodcock, M.D., Director, CDER
Ellis Unger, M.D., Director, Office of Drug Evaluation I, CDER
Luciana Borio, M.D., Chair, Agency Scientific Dispute Process Review Board

FROM: Robert M. Califf, M.D., Commissioner of Food and Drugs

RE: Scientific Dispute Regarding Accelerated Approval of Sarepta Therapeutics’ Eteplirsen (NDA 206488) – Commissioner’s Decision

DATE: September 16, 2016

Overview

The Chair of the Agency Scientific Dispute Process Review Board (SDR Board), Dr. Luciana Borio, has forwarded to me the Board’s recommendation regarding the appeal by Dr. Ellis F. Unger, the Director of the Office of Drug Evaluation I, of Dr. Janet Woodcock’s decision; namely, that Sarepta Therapeutics’ drug eteplirsen (AVI-4658) meets the standard for accelerated approval for treatment of Duchenne muscular dystrophy (Duchenne or DMD) in patients who have a confirmed mutation of the dystrophin gene amenable to exon 51 skipping, which affects about 13 percent of the population with DMD. Duchenne is a rare genetic disorder characterized by progressive muscle deterioration and weakness and is often fatal. Dr. Unger disagrees with Dr. Woodcock’s view and would decline to approve eteplirsen at this juncture.¹

The SDR Board’s memorandum of August 8, 2016 concludes that under the standard for review set out in FDA’s Staff Manual Guide for formal appeals of internal FDA scientific disputes, Dr. Unger had an adequate opportunity to present his scientific concerns within the Center for Drug Evaluation and Research (CDER), and that Dr. Woodcock considered all relevant evidence in making her decision.² In her capacity as Acting Chief Scientist, Dr. Borio also conveyed her own views on the dispute, stating among other things that she does not believe the available data and information support accelerated approval of eteplirsen.³ As the SDR Board’s role was to conduct a procedural review, the SDR Board further recommended that I either conduct a substantive scientific review of the dispute or convene a panel of experts to conduct a scientific review and

¹ Appeal at 1.
² SDR Board Recommendation at 2.
³ Id. at 2, 25-26.
advise the Agency on whether the available evidence for eteplirsen meets the standard for accelerated approval.\(^4\)

I note that, in my understanding, **it is highly unusual for a Center Director’s decision regarding a product application to be appealed to the Commissioner’s office.** Decisions on medical product approvals and clearances are delegated under provisions of Staff Manual Guide 1410 to the appropriate Center Directors and Center staff.\(^5\)

I have read the documents pertinent to Dr. Unger’s appeal, Dr. Woodcock’s final Center decision, and the review and recommendation of the SDR Board. I have performed a thorough review of the basic and clinical science, a review that also comprised a briefing with the review team, including Dr. Unger, and discussions with Drs. Woodcock and Jenkins. Although under the standard for review set forth in Staff Manual Guide 9010.1, I was not required to review the science, I did so in order to properly evaluate the positions of Dr. Woodcock and Unger. **My decision following this review is to defer to Dr. Woodcock’s judgment and authority to make the decision to approve eteplirsen under the accelerated approval pathway, in her capacity as Director of the Center for Drug Evaluation and Research.**

My reasoning and detailed considerations for my decision are given below.

**Examination of the Scientific Dispute**

**Key Points of Agreement**

There is agreement that Dr. Unger’s views and those of the review team were heard in great detail in an environment of open discussion and dissent on multiple occasions. I agree with the SDR Board that there is no basis for overturning Dr. Woodcock’s decision on procedural grounds and Dr. Unger also agrees with this conclusion.

**In addition, the science is not in dispute** beyond the usual types of disagreement that occur when experts review clinical evidence from different perspectives. As discussed in detail below, the evidence evaluation is complicated by the unusual circumstance of the development program, which involved a small subset of children with a rare disease and was characterized by major

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\(^4\) Id. at 2, 27.

\(^5\) Although, as described in Staff Manual Guide 1410.21.1.A., the Commissioner retains authority to make decisions on medical product applications, those decisions are most appropriately vested in the Centers and only the most unusual circumstances would warrant overturning the decision of a Center—including that of a Center Director—on a medical product application. As is set out in the Staff Manual Guide 9010.1 applicable to this matter, FDA has adopted a formal scientific dispute resolution process that emphasizes 1) establishing and maintaining robust dispute resolution processes within the Centers to ensure candid and comprehensive discussion of scientific issues, and 2) a Commissioner’s Office review that focuses on the adequacy of the internal Center scientific dispute process (i.e., whether the Center’s processes were followed, whether the Center considered all relevant evidence bearing on the scientific question at issue, and whether the initiator of the appeal was provided an opportunity to express concerns at all appropriate levels, prior to and including the Center Director). This established dispute resolution process does not contemplate a substantive decision on the disputed issue by the Commissioner.
flaws in the clinical study design, making the judgment on science difficult. The points of agreement include the following:

- DMD is a rare, progressive disease characterized by the virtual absence of functional dystrophin.\(^6\)
- There is no approved therapy for DMD.\(^7\)
- The principal question in this dispute is not whether dystrophin level is an appropriate surrogate endpoint for the purpose of accelerated approval, but whether the quantity of dystrophin produced by eteplirsen is an effect that is reasonably likely to predict clinical benefit, as required under section 506(c)(1)(A) of the Federal Food, Drug, and Cosmetic Act and FDA regulations at 21 CFR 314.510.\(^8\)
- Available preclinical work supports the clinical development of eteplirsen, most notably clear documentation of production of the transcript and the protein in a dose-dependent manner in primates, without measurable toxicity.\(^9\)
- **Major flaws in both the design and conduct of the clinical trials using eteplirsen have made it impossible to use much of the resulting trial data as reliable evidence in regulatory decision-making, including for reasonable extrapolation to clinical care.**\(^10\)
- Despite the flaws in the clinical development program noted above, both Dr. Woodcock and Dr. Unger, as well as the review team, agree that eteplirsen produces measurable increases in dystrophin compared with control.\(^11\) All agree that the amount of dystrophin produced is small compared with expectations at the outset of trials in humans.\(^12\)

Although the gap between expectations and measured increase is not directly relevant to the final decision, the log-order difference has added further uncertainty. If the levels of dystrophin had reached those measured in the setting of Becker muscular dystrophy, there would be much less concern.

- Although there is some disagreement about whether the data support the expression of dystrophin in one study (201/202), there is agreement that the other (study 301) demonstrates clear evidence for dystrophin production. Dr. Unger concludes that there is

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\(^6\) Appeal at 2; SDR Board Recommendation at 2.
\(^7\) Appeal at 2. I note that there is a modest body of evidence suggesting that treatment with corticosteroids yields relatively short-term improvements in function and muscle strength (see Matthews E, et al. Cochrane Database Syst Rev. 2016;(5):CD003725. doi: 10.1002/14651858.CD003725.pub4), but there is no evidence from adequate and well-controlled trials that this therapy has a major effect on the course of the disease.
\(^8\) Appeal at 3; SDR Board Recommendation at 4, 17.
\(^9\) ODEI Decisional Memo, July 2016.
\(^10\) Woodcock Decisional Memorandum at 2-3, 11; Appeal at 4-5, 8-9.
\(^11\) Woodcock Decisional Memorandum at 3; Appeal at 6.
\(^12\) Woodcock Decisional Memorandum at 11.
evidence from one adequate and well-controlled trial, while Dr. Woodcock concludes there is evidence from two adequate and well-controlled trials.\(^\text{13}\)

**Key Points of Disagreement**

There is disagreement about whether the amount of dystrophin protein produced is sufficient to be “reasonably likely” to predict a clinical benefit. The basis for the judgment about “reasonably likely” is subjective and is not explicitly defined in statute or regulations. FDA’s Guidance on Expedited Programs for Serious Conditions – Drugs and Biologics (May 2014) states at page 19 (internal citation omitted):

> Determining whether an endpoint is reasonably likely to predict clinical benefit is a matter of judgment that will depend on the biological plausibility of the relationship between the disease, the endpoint, and the desired effect and the empirical evidence to support that relationship. The empirical evidence may include “... epidemiological, pathophysiological, therapeutic, pharmacologic, or other evidence developed using biomarkers, for example, or other scientific methods or tools.”

I conclude that Dr. Unger and Dr. Woodcock have each exercised reasonable scientific judgment in reaching differing conclusions on whether the effect on dystrophin production seen in the studies in Sarepta’s application reasonably predicts clinical benefit for the relevant subpopulation of Duchenne patients. There is also abundant evidence that Dr. Woodcock heard and read all the scientific evidence, including the detailed views of Dr. Unger and the review team; yet she came to a different conclusion. These differing conclusions are detailed immediately below:

- **Dr. Unger**, the review team, and Dr. Borio have concluded that the demonstrated levels of dystrophin are not “reasonably likely” to predict clinical benefit based on a chain of logic that is well-described in Dr. Unger’s appeal and in Dr. Borio’s summary.\(^\text{14}\) In essence, based on the belief that Becker muscular dystrophy provides a model for Duchenne because the dystrophin is similar to that produced with eteplirsen, Dr. Unger concludes that functional protein in the range of 10% of normal levels would be needed to provide evidence that would make it “reasonably likely” that changes in the surrogate would predict clinical benefit.\(^\text{15}\) The use of Becker muscular dystrophy as a model for DMD is an extrapolation, but a rational one in the absence of validation of dystrophin as a surrogate.

- Dr. Unger also finds that the results of the eteplirsen clinical trials to be inadequate for supporting the conclusion that there is any relationship between measured levels of dystrophin and improvement in function within the trial data sets. Making certain

\(^{13}\) Woodcock Decisional Memorandum at 2-5; Appeal at 4-6.  
\(^{14}\) Appeal at 4, 11-20; SDR Board Recommendation at 25.  
\(^{15}\) Appeal at 12-15.
assumptions, he provides plots and calculations that he interprets as showing that higher dystrophin levels are not associated with improved function in the eteplirsen trials.\textsuperscript{16}

- Dr. Borio fundamentally agrees with Dr. Unger’s conclusion, and Dr. Jenkins concurs with Dr. Unger.\textsuperscript{17}

- Dr. Woodcock finds that using “...the greatest flexibility possible for FDA while remaining within its statutory framework,” eteplirsen is “...reasonably likely to predict clinical benefit.”\textsuperscript{18} Her conclusion is based on a view that the data from both Study 201/202 and Study 301 are from adequate and well-controlled trials and that, although imperfect, they adequately meet criteria to include as affirmation of a drug effect that is reasonably likely to predict clinical benefit. She points out the many uncertainties about extrapolating from a particular level of a surrogate to clinical benefit when that surrogate is not yet proven, including complexities of assay validation, determining whether protein is functional, and also the extraordinary difficulty of knowing how the amount of protein might affect functional outcome over time and within the context of the multidimensional nature of protein interactions in complex cellular and subcellular functions. She finds no rational basis for identifying a specific threshold value for dystrophin levels that would be needed to support a determination that a particular level is “reasonably likely” to predict clinical benefit.\textsuperscript{19} Furthermore, she provides some post-hoc calculations from the eteplirsen clinical trials that she regards as supportive, though not definitive, evidence that higher levels of dystrophin are associated with greater function.

She is clearly employing and interpreting the full range of appropriate information, comprising a “totality of evidence” approach in determining that the clinical trials demonstrated an effect on a surrogate endpoint that is reasonably likely to predict clinical benefit. Because of the uncertainties in this situation with a surrogate that has not been validated, it is clear that Dr. Woodcock’s decision also utilized the flexibility afforded under the relevant statutory provisions, including consideration of the life-threatening nature of the disease and the lack of alternative treatments.

**Conclusions Regarding the Scientific Dispute**

**I conclude that qualified experts with extensive experience in FDA decision-making and stellar track records can assimilate the same scientific evidence and disagree about the extrapolation to whether the evidence supports a conclusion that the treatment has an effect that is “reasonably likely” to predict clinical benefit.** Both Dr. Unger and Dr. Woodcock have drawn upon a deep level of knowledge and practical experience in deriving their conclusions, and their documents reflect strong convictions and profound concern both for the

\textsuperscript{16} Id. at 15-18.
\textsuperscript{17} SDR Board Recommendation at 15, footnote 94.
\textsuperscript{18} Woodcock Decisional Memorandum at 12.
\textsuperscript{19} Id. at 9.
well-being of the patients and families with DMD and for the preservation of the FDA’s mission to protect and promote public health. That said, the history of the FDA includes a consistent precedent of final decision-making about medical products at the Center level. Overruling the Center Director is exceedingly rare and, in my view, would be appropriate only if the Center Director’s decision could not be supported by the available data and information. In the present case, the scientific uncertainties lead to a situation in which the decision is a matter of reasoned expert opinion and judgment.

Given that I do not have technical expertise beyond those already involved in this decision and the record contains adequate evidence to support her conclusion, I defer to the judgment of the Center Director to approve eteplirsen under accelerated approval with the stipulations delineated in her Decisional Memo.

Additional Concerns

The SDR Board expresses concerns based on Dr. Unger’s appeal and on interviews the Board conducted in its procedural review about the level of involvement of the Center Director in the review of the New Drug Application for eteplirsen. The following four points of concern were raised by Dr. Unger and cited by the SDR Board:

1. Intense involvement of the Center Director in early stages of review;
2. Extensive involvement in planning and participating in the Advisory Committee meeting to consider eteplirsen, held on April 25, 2016;
3. Initial decision by Dr. Woodcock on May 4, 2016 to approve before the review team had finalized its process for decision-making; and
4. Final decisional memorandum by Dr. Woodcock completed before Dr. Unger finalized his own decisional memo.

The SDR Board expresses concern about Dr. Woodcock’s “extensive, early involvement in the review process” and states that “her involvement here appears to have upended the typical review and decision-making process.” Moreover, the Board cautions that “…care should be taken to avoid the appearance of interfering with the integrity of scientific reviews at the lower levels of a Center.” The SDR Board concludes that “Dr. Woodcock herself was the one who conducted that review and resolved the conflict in her own favor.”

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20 SDR Board Recommendation at 23.
21 Id.
22 Id. at 27.
The concerns raised by Dr. Unger and by the SDR Board require that I evaluate the role of the Center Director. While there are many aspects of this situation that are unusual, leading to a rare formal dispute between a review team and a Center Director, I note the following points:

- Dr. Woodcock's management style has been "hands on" during her entire career at the FDA. She is well-known for interacting with staff at all levels and expressing her opinions. Indeed, complex and difficult cases often lead to early interactions with leaders, and as described below, frequent meetings and discussions along the way are common in CDER. This development program may represent a point of particular focus for Dr. Woodcock with the result that her involvement was more intensive than usual and correspondingly had an effect upon the review team, but such a focus does fit within a longstanding management approach.

- At the same time, under Dr. Woodcock's leadership and in conjunction with the leadership of Dr. John Jenkins in the Office of New Drugs, multiple mechanisms have been established for ongoing and interim discussions of evolving drug development programs and decision-making. These sessions, such as the Medical Policy Council, weekly senior staff meetings, the use of frequent Center Director briefings (in this case at least 14), and external advisory committee meetings are known for their exchange of ideas and welcoming of differences of opinion. Within this context it is also understandable that when so much is at stake with this degree of uncertainty, passionate debate can occur.

- An additional factor in this situation is the emergence of patient-centered drug development and the extensive interactions with the patient community as part of the overall environment for development and decision-making. While the appropriate methods for patient-centered drug development are evolving, the fact that DMD involves vulnerable children with a life-threatening illness and understandably concerned parents produces significant pressure on all involved. This dynamic is well reflected in Dr. Unger and Dr. Woodcock's documents. With a significant history dating back to the development of drugs for HIV/AIDS, patient-focused drug development is not an entirely new component of FDA's regulatory process, and it remains an explicit CDER priority in the current era.

- While others might direct and manage the organization and interact with patient and family communities in a different manner than Dr. Woodcock, it is difficult to argue that CDER has been unsuccessful under her leadership. A vast array of new drugs approved during her tenure is benefitting patients, including a host of significant advances using a variety of expedited programs. Further, this litany of therapeutic successes has been accomplished without compromising overall standards. Under Dr. Woodcock's leadership, commitment to due process and mutual review of scientific data have been major parts of CDER culture and are making a significant impact on drug development.
• It is inevitable that in some of these situations, highly qualified experts will disagree. In the face of profound changes in science and social interactions related to drugs, under Dr. Woodcock’s leadership CDER enjoys broad public support, largely due to the constant, healthy atmosphere of transparency and debate that characterizes the documentation in this appeal. A review of Dr. Woodcock’s record reveals extraordinary courage in the face of extreme pressure on many occasions, including from Congress, the press, patient and patient advocacy groups, and industry. She has taken and supported unpopular decisions when appropriate and is well-known for not relenting to pressure. Further, I find no pattern that indicates that this decision is part of a trend for lowering the standard for drug approval—a trend that would be unacceptable in any event.

Conclusions Regarding Additional Concerns

Overall, while I recognize the strain created by political and public pressures, given Dr. Woodcock’s well-documented history of not bowing to such influences and a record in this case showing her close consideration of all relevant scientific evidence, I do not find that she deviated from her responsibilities as Center Director, nor do I find that she succumbed to pressure from the patient community, the public, the press, or others. Further, I do not find the general pattern of discourse and involvement to be atypical for Dr. Woodcock’s management of the Center, nor do I find that her conduct was in conflict with the job requirements for Center Directors at the FDA.

Additional Context: Accelerated Approval

It is important to note that the debate about this application is taking place in the context of an accelerated approval. Even under the best circumstances, accelerated approval may lead to decisions that are not verified upon further examination. These limitations are a reason accelerated approval is available only for a limited group of drugs: those intended to treat serious or life-threatening illnesses when the drug is expected to provide a meaningful benefit over existing therapy. In accelerated approvals, the surrogate is not a validated surrogate. As noted in FDA’s Guidance on Expedited Programs for Serious Conditions – Drugs and Biologics, page 17:

> For purposes of accelerated approval, a surrogate endpoint is a marker, such as a laboratory measurement, radiographic image, physical sign, or other measure, that is thought to predict clinical benefit, but is not itself a measure of clinical benefit. Depending on the strength of the evidence supporting the ability of a marker to predict clinical benefit, the marker may be a surrogate endpoint that is

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23 I was troubled by statements on page 16 of the SDR Board memo that Dr. Woodcock’s decision to approve eteplirsen may have been inappropriately motivated by concerns over the sponsor’s financial well-being. To address to my own satisfaction any questions that Dr. Woodcock’s statements in the SDR Board memo might raise, I have discussed this issue directly with Dr. Woodcock, who said that she was aware of the financial pressures on the company, but that her decision was based on the science. Based on the record and our conversation, I am satisfied that her decision is indeed based on her scientific evaluation of the evidence.
known to predict clinical benefit (a validated surrogate endpoint that could be used for traditional approval), a surrogate endpoint that is reasonably likely to predict a drug’s intended clinical benefit (and that could therefore be used as a basis for accelerated approval), or a marker for which there is insufficient evidence to support reliance on the marker as either kind of surrogate endpoint (and that therefore cannot be used to support traditional or accelerated approval of a marketing application). 24

Dr. Unger’s and Dr. Borio’s significant concerns about the implications of approving eteplirsen on the basis of the current data, even under the accelerated approval pathway, are evident. 25 As noted previously, Dr. Woodcock has explained that approval here will rely on “....the greatest flexibility possible for FDA.” 26 The record amply reflects that the evidence here is not as strong as everyone involved in this dispute wishes it were. The record also reflects, however, that Dr. Woodcock has fully considered the patient population, lack of alternative therapies, and relevant information and analyses, and has concluded that the data are sufficient to meet the accelerated approval standard. Therefore, while I understand the concerns expressed by Drs. Unger and Borio regarding the implications of lowering of the standard for approval, I defer to Dr. Woodcock’s conclusion that accelerated approval in this case does not represent such a lowering of the bar.

Opportunities for Process Improvement

I agree that there are many aspects of the history of eteplirsen that we must avoid in the future. Given the distinguished careers, time-proven expertise, and sincere concerns of Drs. Unger, Borio, Jenkins, and Woodcock, it is critical to review the following key lessons from this experience:

- All reviewers point to serious flaws in the eteplirsen drug development program. I personally have had many experiences in drug development and the assessment of therapeutics; it is common for problems to emerge that can be identified easily in

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24 More expansive discussion of these important issues on definitions of biomarkers and surrogates is included in a joint document from FDA and the National Institutes of Health, which can be found at: http://www.ncbi.nlm.nih.gov/books/NBK326791.

25 In her capacity as Acting Chief Scientist, Dr. Borio notes: “Granting accelerated approval here on the basis of the data submitted could make matters worse for patients with no existing meaningful therapies—both by discouraging others from developing effective therapies for DMD and by encouraging other developers to seek approval for serious conditions before they have invested the time and research necessary to establish whether a product is likely to confer clinical benefit.” Dr. Unger concludes: “If we were to approve eteplirsen without substantial evidence of effectiveness, or on the basis of a surrogate endpoint with a trivial treatment effect, we would quickly find ourselves in the position of having to approve a myriad of ineffective treatments for groups of desperate patients. In essence, allowing marketing based on desperation, patient lobbying, and the desire and need of hope. If we were to turn the clock back to the days prior to the 1962 Kefauver-Harris Amendments to the Federal Food, Drug, and Cosmetic Act, the damage to society and the field of evidentiary medicine would be enormous.” Dr. Jenkins expressed the same concerns, both in written documents and in follow-up discussions I have had with him.

26 WoodcockDecisional Memorandum at 12.
retrospect. Clinical development involves numerous human decisions and compromises engendered by the fact that clinical trials involve human research participants who must be respected independently of the many others who design, conduct and judge the research. Furthermore, the diverse interests of sponsors, patients and families, investigators, and regulators must be melded into a few protocols for human studies, so that no protocol represents 100% agreement. Accordingly, any retrospective criticism should be expressed with humility. However, the flaws in the eteplirsen program are serious and worthy of attention by others developing drugs for serious rare diseases.

- Specifically, the poor quality of many of the biopsies and the failure of the sponsor to implement a high-quality procedure for assay validation led to a situation in which only a fraction of the data could be used to make the regulatory decision. Given the serious nature of the disease and the invasiveness of the procedures, any studies must be conducted according to the highest standards, so that each child and parent who volunteers can be confident that they have contributed as much as possible to the generalizable knowledge needed to provide effective treatment based on high-quality evidence. Such attention to standards of quality in study conduct is a critical element of respect for research participants.

- Further, all reviewers agree that had the sponsor conducted properly-controlled, randomized trials with dose escalation from the beginning, we would by now likely have access to definitive information that would have resolved the disagreement. Dr. Woodcock points out that “…[t]here is no such thing as an ‘exploratory study’ for a serious, life-threatening disease without therapeutic options. Randomization should be performed very early in the development program and open-label studies should be avoided.” 27 Time after time, we see the over-hyping of preclinical results playing into misguided arguments that prevent the generation of high-quality evidence because of unrealistic expectations of benefit, which ultimately fosters continued uncertainty about the clinical value of therapeutics.

- It is unfortunate that the sponsor touted an academically based study that had unreliable measures of the assay, thereby greatly overstating the degree of protein expression in the follow-up biopsies. Blinded experts assembled by the FDA fundamentally debunked this study, which has yet to be retracted and continues to be cited. 28 Dr. Woodcock identified the lack of a reliable assay as the primary defect in this “seriously deficient” development program, and Dr. Unger comments multiple times on the uncertainties in the assay and the manner in which poor methodology undermined the results presentation. 29 It is critical that we continue to improve the entire pipeline of translational research to introduce more rigorous and reliable methods, even in academically-conducted

27 Woodcock Decisional Memorandum at 11.
28 In view of the scientific deficiencies identified in this analysis, I believe it would be appropriate to initiate a dialogue that would lead to a formal correction or retraction (as appropriate) of the published report.
29 Id.
translational research. Likewise, it is equally important that we continue to work on ways to purge discredited research in a manner that reduces inappropriate citation and follow-on research based on the incorrect assumption of the accuracy of the precedent studies.

- Dr. Unger also points out that data from primate studies suggest that a substantial increase in dose (approximately a log order) might well produce the 10% of normal dystrophin levels that Dr. Unger feels would meet criteria for an effect that is "reasonably likely to predict clinical benefit." This view that much higher doses are likely to be beneficial is shared across the entire FDA hierarchy, yet studies have not been done in humans at higher doses. However, the FDA must make a decision based on available data.

- As Drs. Unger, Woodcock, and Borio all point out, the risk of lowering the bar for new drug approval is a serious concern. We must remember that over 90% of drugs that enter clinical trials do not make it to market, usually due either to inadequate beneficial effect or unexpected toxicity. Lowering the regulatory hurdle could expose unsuspecting patients to the harmful effects of these drugs that would have failed if proper development had been done. But the statute and regulations clearly demarcate accelerated approval as a special situation in which a range of evidence from various sources and unvalidated surrogates may be used to determine whether the demonstrated effect on a surrogate endpoint is reasonably likely to predict clinical benefit, requiring an additional judgment on the part of the FDA. Thus, I am confident that this unique situation will not set a general precedent for drug approvals under the accelerated approval pathway, as the statute and regulations are clear that each situation must be evaluated on its own merits based on the totality of data and information.

The Path Forward

Given the approval status of eteplirsen, it is critical for the well-being of patients with DMD that the course of action fulfills the intent of accelerated approval and that the very best methods are used. As required for post-marketing studies for products approved under the accelerated approval program, the sponsor must conduct the required confirmatory trial with due diligence to evaluate whether eteplirsen has the predicted clinical benefit. It is notable that Dr. Unger and Dr. Woodcock agreed on several key points regarding further study of eteplirsen, regardless of the approval decision:

- The low doses currently employed are regarded as a starting point, as it seems likely that significant increases in dose could lead to desirable ranges of dystrophin production. Accordingly, a dose-finding study at much higher doses (as much as a log order increase)

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30 Appeal at 27.
is needed to find the dose most likely to lead to maximal clinical improvement, as will be reflected in the approval letter for eteplirsen:\footnote{Draft Approval Letter for eteplirsen, as of September 9, 2016.}

\begin{quote}
In order to verify the clinical benefit of eteplirsen, conduct a 2-year randomized, double-blind, controlled trial of eteplirsen in patients who have a confirmed mutation of the DMD gene that is amenable to exon 51 skipping. Patients should be randomized to the approved dosage of eteplirsen (30 mg/kg weekly) or to a dosage that provides significantly higher exposure, e.g., 30 mg/kg daily. The primary endpoint will be the North Star Ambulatory Assessment.
\end{quote}

Dr. Unger points out that Study 301 could be converted to a randomized trial in which one arm remains on the current dosing regimen and the other(s) receive higher doses in the range that might be expected to produce much higher dystrophin levels.\footnote{Appeal at 27.} A study with only a modest increase in dose that found no difference would be non-informative. Accordingly, the difference in doses in a post-approval trial should be enough to create clear separation in dystrophin levels.

- Dr. Woodcock notes that the sponsor is also conducting a randomized trial of eteplirsen versus no therapy in other forms of DMD.\footnote{Woodcock Decisinal Memorandum at 10.} The utmost attention should be paid to optimizing the methodological rigor of this trial and the trial evaluating higher doses discussed above.

- It is essential that the clinical and patient communities not be misled by exaggerated claims, given the poor quality of the studies in the sponsor’s application and the fact that the approval is based on a non-validated surrogate and that clinical benefit has not yet been established. The applicable statutory and regulatory provisions governing accelerated approval, which require sponsors to submit promotional materials to FDA for pre-dissemination review, should be helpful in this regard.

\section*{Summary}

In conclusion, I defer to Dr. Woodcock in her role as Center Director to make the decision to approve eteplirsen under the accelerated approval provisions. I find merit and reason on both sides of the disagreement, and despite the intensity of the argument, I believe that the quality of thinking on both sides reflects the importance of clinical and scientific expertise coupled with due process within the FDA. I find no basis for a view that Dr. Woodcock was unduly influenced by involvement with the patient community or other external pressures, and note that our understanding about how to include patients in the regulatory process is evolving. In addition, serious shortcomings present in the eteplirsen development program should not be allowed to establish a broad precedent for therapeutic development in rare diseases. In the end, we have
significant agreement on the science, but a disagreement on the integration of all the evidence as to whether the small changes in dystrophin levels induced by these doses of eteplirsen are “reasonably likely” to predict clinical benefit. Considering that a substantially flawed development program contributed to the difficulty coming to resolution in this case, we must redouble our efforts to move the therapeutic development ecosystem to use methods that will produce high-quality evidence from the outset.

For the reasons set forth above, CDER’s final decision, as set forth in Dr. Woodcock’s July 14, 2016 Memorandum, is upheld. This matter is remanded to CDER for action consistent with this decision.

Robert M. Califf, M.D., Commissioner of Food and Drugs

[Signature] Sept. 16th, 2016