DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Office of the Commissioner

Date: August 8, 2016

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

From: Luciana Borio, M.D.
Acting Chief Scientist

Luciana Borio -A

Digitally signed by Luciana Borio -A
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Date: 2016.08.08 20:00:37 -04'00'

Subject: Scientific Dispute Resolution Appeal regarding Eteplirsen

This matter is before the Office of the Commissioner on an appeal submitted by Ellis Unger, M.D., Director of the Office of Drug Evaluation I (ODE-I) (the initiator), under Staff Manual Guide 9010.1, "Scientific Dispute Resolution at FDA" (the SDR-SMG). In his scientific dispute resolution (SDR) appeal, dated July 18, 2016, Dr. Unger challenges the basis for a decisional memorandum issued by Janet Woodcock, M.D., Director of the Center for Drug Evaluation and Research (CDER). Dr. Woodcock's decisional memorandum concludes that a new drug application (NDA) submitted by Sarepta Therapeutics Inc. (Sarepta) for eteplirsen, a drug intended to treat Duchenne muscular dystrophy (DMD), meets the standard for accelerated approval under 21 CFR § 314.510. Specifically, Dr. Woodcock's memorandum states that the data submitted in support of the NDA establishes "increased dystrophin protein production, a surrogate endpoint [for DMD] that [she] conclude[s] is reasonably likely to predict clinical benefit."[1] Dr. Unger states that he disagrees with Dr. Woodcock's decisional memorandum because he does not believe "the findings on the dystrophin surrogate endpoint are reasonably likely to predict clinical benefit."[2]

Upon receipt of the appeal from Dr. Unger, in accordance with the SDR-SMG, the Office of the Chief Scientist convened the Agency Scientific Dispute Process Review Board (the SDR Board), a standing committee, which I chair, whose role in evaluating the appeal is to conduct a review of the processes used in the Center to render a decision on the scientific dispute at issue.[3] Under the SDR-SMG, "The goal of this review is to determine if the processes followed in the Center fully considered all relevant evidence and provided the initiator with an opportunity to express his or her concerns at all appropriate levels, prior to and including the Center Director."[4] My role in the process, as Chair of the SDR Board, is to provide a recommendation to you, as Commissioner of Food and Drugs, with respect to "whether a Center failed to follow its processes and/or did not provide an adequate opportunity to the initiator to express his or concerns; [whether] all relevant evidence bearing on the scientific question at issue has been considered; and[] whether the dispute should be remanded to the Center Director."[5] The written

[1] Woodcock Decisional Memorandum at 1.
[2] Appeal at 3.
[3] SDR-SMG at 3. ("The Agency Scientific Dispute Process Review Board (hereafter Board) is a standing committee comprised of representatives of the Office of Accountability and Integrity, Ombudsmen from all Centers and the agency (or officials so designated) and representative(s) from the Office of the Chief Scientist. The Board is chaired by the Chief Scientist.").
[4] *Id*. at 12.
[5] *Id.* at 5.

recommendation must reflect the SDR Board's underlying rationale, along with minority views among the members, for those findings.[6]

In conducting its evaluation, the SDR Board reviewed pertinent aspects of the Center's administrative file for the eteplirsen NDA and interviewed Dr. Unger, Dr. Woodcock, one member of the review team for the NDA, who requested anonymity, and Virginia Behr, the Ombudsman for CDER. Based on its review, the SDR Board has determined that the processes followed by CDER provided Dr. Unger with an adequate opportunity to present his scientific views and that CDER considered all relevant evidence. As Chair of the SDR Board, I therefore recommend that you do not remand this matter to the Center Director for further action.[7] However, there are additional considerations meriting your attention, which I describe below. Furthermore, the SDR Board encourages you to conduct a thorough substantive review of the scientific dispute in this matter or, in the alternative, to convene a panel of relevant experts to conduct such a review and provide advice to the agency and you, as Commissioner, on whether the evidence of the effect of eteplirsen on the surrogate endpoint is reasonably likely to predict clinical benefit.

BACKGROUND

1. Eteplirsen and DMD

Dr. Unger provides an overview of eteplirsen and DMD in his appeal.[8] In short, DMD is a genetic disorder with catastrophic effects on its sufferers:

> [DMD] is an X-linked recessive neuromuscular disorder caused by mutations of the dystrophin gene[,] . . . [which] disrupt the messenger ribonucleic acid (mRNA) reading frame [and] lead[] to the absence or near-absence of dystrophin protein in muscle cells. . . . Absence of dystrophin leads to muscle damage, with replacement by fat and collagen. . . [and a concomitant] loss of physical function in childhood and adolescence, with premature death from respiratory and/or cardiac failure in the second to fourth decade.[9]

There are no FDA-approved therapies for DMD.[10] Sarepta has designed eteplirsen to target the pre-mRNA transcripts of the dystrophin gene so that exon 51 is excluded from the resulting mRNA:[11]

> [B]y restoring [] the mRNA reading frame, a 'truncated' but nevertheless partially functional form of the dystrophin protein can be produced by muscle cells, delaying disease progression. Similar truncated dystrophin is found in a less severe form of muscular dystrophy, Becker Muscular Dystrophy (BMD). In essence, the drug is hoped to induce production of sufficient Becker-type dystrophin to slow the progression of the disease. This drug is specific for exon 51 mutations, a subset of the mutations that cause DMD. If approved, the drug

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[6] *Id.*at 13.
[7] *See id.* ("The Commissioner will review the [SDR Board's] recommendation and render a final decision on . . . whether the dispute should be remanded to the Center Director for corrective action" and "work with the Center Director to determine what corrective actions must be taken, if any.").
[8] Unless otherwise indicated, Drs. Unger and Woodcock appear to agree as to the background provided in this section.
[9] Appeal at 2.
[10] *Id.*
[11] The charity, Muscular Dystrophy UK, has a nice description of the technology underpinning eteplirsen, which can be accessed at: http://www.musculardystrophyuk.org/progress-in-research/background-information/what-is-exon-skipping-and-how-does-it-work/.

> would be indicated for ~13% of the overall DMD patient population. Eteplirsen has not received marketing authorization from any regulatory authority, and no similar drugs are approved.[12]

In attempting to establish that eteplirsen is safe and effective for the treatment of DMD, and thus meets one of the standards for approval in the Federal Food, Drug, and Cosmetic Act (FD&C Act), Sarepta has submitted data from three clinical studies:

> Study 201 was a single-center, double-blind, placebo-controlled study in 12 patients with DMD. Patients were randomized (1:1:1) to eteplirsen 30 mg/kg/week, eteplirsen 50 mg/kg/week, or placebo (4 patients per group). After 24 weeks, the 4 patients originally randomized to placebo were re-randomized to eteplirsen 30 mg/kg/week (n=2) or eteplirsen 50 mg/kg/week (n=2). The trial was eventually extended to an open-label phase (Study 202) where all patients received eteplirsen, although investigators and patients remained blinded to dose. These patients have continued to receive eteplirsen for more than 4 years. This continuous study is referred to as Study 201/202. Study 301 is an externally controlled study where all patients are receiving open-label eteplirsen, 30 mg/kg, by weekly infusion. The study is ongoing and still accruing patients. Interim data were obtained from 13 patients in this study.[13]

Dr. Unger further explains:

> The endpoints for [the three] studies can be broadly divided into those that aim to show changes in physical performance, e.g., walking speed, rise time from the floor, muscle function; and those that aim to show effects on production of dystrophin in skeletal muscle – the surrogate endpoint. Dystrophin was quantified in this development program using two methods: Western blot and immunohistochemistry.[14]

Immunohistochemistry (IHC) analysis looks at thin slices of muscle biopsies to see if dystrophin is present or absent. Each muscle fiber that shows any amount of dystrophin is counted as positive, regardless of the actual quantity of dystrophin present. Western blot analysis assesses how much dystrophin is present.

For Study 201/202, Sarepta submitted Western blot and IHC analysis evaluating proteins in muscle samples obtained from the twelve patients before the study and then again at twelve, 24, and 48 weeks.[15] "The Western blots submitted by the applicant for Study 201 were oversaturated, unreliable, and uninterpretable."[16] Because CDER also determined that the conditions under which the original IHC analysis was performed were inadequate, including that the reader was not masked to sequence and time, the Center requested a re-reading of the stored images by three masked pathologists under different conditions.[17] The IHC results from the reread were not nearly as favorable, as compared to the initial IHC results reported by Sarepta.

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[12] Appeal at 2.
[13] *Id.*
[14] *Id.*
[15] *Id.* at 4, 8.
[16] *Id.* at 4.
[17] Unger Decisional Memorandum at 12-13.

> The re-read showed a nominally statistically significant increase in dystrophin in response to eteplirsen for the low dose group, but not the high dose group[] (. . . [T]he type-I error rate was not controlled for multiplicity.)[18] Moreover, for the 4 patients who had received placebo through Week 24 and then switched to eteplirsen, there was no increase in dystrophin at Week 48.[19]

For Study 201/202, CDER also worked with Sarepta to improve the Western blot assays, and researchers performed repeat biopsies on eleven of twelve patients at Week 180.[20] Only three of the eleven patients had stored baseline samples that were adequate for evaluation, and so baseline samples were obtained from six additional patients external to Study 201/202.[21] Dr. Unger also notes that all baseline samples were obtained from a different muscle group than the samples obtained at Week 180.[22] Based on its own analysis of the IHC data, Sarepta claimed a remarkable increase of dystrophin immunostaining at Week 180: from 1.1% ±1.3% positive muscle fibers at baseline to 17.4% ± 10.0% positive fibers at Week 180.[23] The Western blot analysis resulted in Week 180 dystrophin levels that were small, with a mean increase of only 0.93% of normal dystrophin levels in the muscle fibers.[24] Dr. Unger remarked that the lack of concordance between the IHC and the Western Blot results is "striking" and also noted that FDA did not verify the integrity of the IHC results.[25] As previously noted, each muscle fiber that shows any amount of dystrophin is counted as positive in IHC, regardless of the actual quantity of dystrophin present.

As noted above, Study 301 is an ongoing study. For purposes of its review of the NDA, CDER requested that Sarepta perform Western blot analysis on samples obtained from 13 patients enrolled in the study.[26] The analysis compared paired biceps samples: baseline samples and samples obtained at 48 weeks, after 48 weeks of treatment with 30 mg/kg of eteplirsen infusion.[27] Dr. Woodcock told the SDR Board that representatives from CDER were present in the laboratory for the Western blot analysis and oversaw the procedures and controls. The Western blot analysis showed a statistically significant increase in dystrophin, ranging in an increase from 0.22% to 0.32% of normal.[28] It should be noted, however, that a statistically significant increase in dystrophin, the surrogate endpoint, of an exceptionally small magnitude does not imply clinical benefit, which is the issue at the core of Drs. Unger and Woodcock's scientific disagreement.

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[18] That is, with respect to time points of assessment and the 2 doses tested.

[19] Appeal at 8-9. Of note, in her decisional memorandum, Dr. Woodcock rejected the findings in both the original and second evaluation of the images: "Much of the controversy over the adequacy of these assessments relates to the fact that rigorously validated assays were not used to evaluate the initial 3 muscle biopsies, apparently resulting in overestimation of the various readouts and some irreproducibility of IHC and Western blot dystrophin assays. For these reasons, I do not discuss or rely upon the results of these earlier assays, or on re-reads of them." (Woodcock Decisional Memorandum at 2). She explained to the SDR Board that, after consultation with others in CDER, she does not view IHC results standing alone as a valid method to evaluate dystrophin levels.

[20] Appeal at 5.

[21] *Id.* at 5, 9.

[22] *Id* at 5. Dr. Unger clarifies in his decisional memorandum that the baseline biopsies were from the biceps muscle, the Week 180 biopsies from the deltoid muscle. (Unger Decisional Memorandum at 17).

[23] Appeal at 9. As discussed below, however, Dr. Unger does not believe that those results are reliable.

[24] *Id* at 5.

[25] *Id.* at 9-10.

[26] *Id.* at 6. Dr. Unger states that the biopsies were obtained from 13 patients but only reports the data as to 12 patients. "There was one patient for whom none of the values met the acceptance criteria [for the Western blot assay]." (Unger Decisional Memorandum at 21).

[27] Appeal at 6.

[28] *Id*.

2. Legal Standard for Accelerated Approval and Patient Perspectives

On December 11, 1992, on the basis of its broad statutory authority to approve drugs under the FD&C Act, FDA issued regulations providing for accelerated approval of drugs.[29] Under 21 CFR § 314.510, FDA may grant accelerated approval for a drug based on a surrogate endpoint under certain circumstances:

> FDA may grant marketing approval for a new drug product on the basis of adequate and well-controlled clinical trials establishing that the drug product has an effect on **a surrogate endpoint that is reasonably likely**, based on epidemiologic, therapeutic, pathophysiologic, or other evidence, **to predict clinical benefit** or on the basis of an effect on a clinical endpoint other than survival or irreversible morbidity. Approval under this section will be subject to the requirement that the applicant study the drug further, to verify and describe its clinical benefit, where there is uncertainty as to the relation of the surrogate endpoint to clinical benefit, or of the observed clinical benefit to ultimate outcome. Postmarketing studies would usually be studies already underway. When required to be conducted, such studies must also be adequate and well-controlled. The applicant shall carry out any such studies with due diligence.[30]

The preamble to the proposed rule defines "surrogate endpoint" as follows:

> A surrogate endpoint, or "marker," is a laboratory measurement or physical sign that is used in therapeutic trials as a substitute for a clinically meaningful endpoint that is a direct measure of how a patient feels, functions, or survives and that is expected to predict the effect of the therapy. For example, elevated cholesterol and hypertension, two surrogate endpoints, are important because they are risk factors for coronary and cerebral artery disease; but it is the impact of the diseases (e.g., angina, congestive heart failure after a heart attack, paralysis after a stroke, or sudden death) that is important to the patient.[31]

In 2012, Congress passed the Food and Drug Administration Safety and Innovation Act (FDASIA). Section 901 of FDASIA amended the FD&C Act to provide FDA with specific authority to grant accelerated approval to drugs for serious conditions.[32] Section 506(c) of the FD&C Act now largely tracks language in the regulations issued by FDA in 1992. Section 901 of FDASIA also added current section 506(e) to the FD&C Act, which clarifies that the amendments were "intended to encourage [FDA] to utilize innovative and flexible approaches to the assessment of products under accelerated approval" but that "[n]othing in this section shall be construed to alter the standards of evidence under subsection (c) or (d) of section 505 (including the substantial evidence standard in section 505(d) of [the FD&C Act]."[33]

Section 901 of FDASIA also directed FDA to issue guidance to industry on the development of

[29] 57 Fed. Reg. 58942 (Dec. 11, 1992).
[30] Emphasis added.
[31] 57 Fed. Reg. 13234, 13235 (Apr. 15, 1992).
[32] FDASIA, PL 112-144, July 9, 2012, 126 Stat. 993.
[33] *Id.*

drugs for accelerated approval and required consideration of the following:

> In developing the guidance . . . [FDA] shall consider how to incorporate novel approaches to the review of surrogate endpoints based on pathophysiologic and pharmacologic evidence in such guidance, especially in instances where the low prevalence of a disease renders the existence or collection of other types of data unlikely or impractical.[34]

Section 1137 of FDASIA further directs FDA to:

> develop and implement strategies to solicit the views of patients during the medical product development process and consider the perspectives of patients during regulatory discussions, including by—(1) fostering participation of a patient representative who may serve as a special government employee in appropriate agency meetings with medical product sponsors and investigators; and (2) exploring means to provide for identification of patient representatives who do not have any, or have minimal, financial interests in the medical products industry.[35]

In May 2014, FDA finalized a guidance on "Expedited Programs for Serious Conditions — Drugs and Biologics." The Guidance provides general information on the evidence that the agency considers in determining whether to grant accelerated approval.[36] The Guidance clarifies that assessing a surrogate endpoint hinges on understanding both the disease process and the relationship between the drug's effect and the disease process.[37] With respect to the latter, the Guidance states:

> The extent to which a drug's effect on the surrogate endpoint is known to predict an effect on the disease either because the effect is on the causal pathway or correlates with clinical outcomes is critical. Sometimes this relationship can be assessed epidemiologically[,] but it is most persuasively established by knowing that a drug that affects the surrogate endpoint also affects a clinical outcome.[38]

The Guidance also provides some insight on how the agency exercises its judgment in evaluating surrogate endpoints when little is known about how an effect on a surrogate endpoint might affect clinical endpoints:

> Particularly in rare diseases, there may be limited information in the literature, lack of in-depth epidemiological or historical data, and little or no experience with other drugs to inform the interpretation of surrogate endpoints or intermediate clinical endpoints. FDA may consult with external experts on surrogate endpoints and intermediate clinical endpoints where there is a lack of historical data for a given disease.[39]

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[34] *Id.*
[35] *Id.*
[36] Expedited Programs Guidance at 19-22.
[37] *Id.* at 20-22.
[38] *Id.* at 21.
[39] *Id.* at 21-22.

FDA obtains patient perspectives through a variety of avenues, "such as open public hearings on specific diseases or drug development issues, and as speakers at FDA-sponsored conferences and workshops."[40]

3. SDR-SMG and CDER's SDR-SOPs

The Office of the Commissioner issued the SDR-SMG on January 13, 2009. Its stated purpose is "to improve the process of internal scientific dispute resolution[] and to encourage open communication throughout the agency."[41] The SMG "encourages the resolution of scientific disputes at the working level in the organization, starting with the frontline employees and their immediate supervisors or team leaders" and cautions that the "agency's appeals process for scientific disputes is not a replacement for robust and fair Center-level processes."[42] As noted above, the SDR-SMG provides for submission of SDR appeals to the Office of the Commissioner and outlines the process and standards for evaluating such appeals. Under the SDR-SMG, the SDR Board evaluates whether "the processes followed in the Center fully considered all relevant evidence and provided the initiator with an opportunity to express his or her concerns at all appropriate levels, prior to and including the Center Director."[43] As Chair of the SDR Board, the Chief Scientist then provides a written recommendation on those issues to the Commissioner, who renders a final decision on whether the scientific dispute should be remanded to the Center for further action.[44]

In addition to outlining the process for elevating scientific disputes to the Office of the Commissioner, the SDR-SMG details the agency's "requirements for the minimum standards for scientific dispute resolution processes in the Centers" and provides a collection of non-mandatory "best practice[s]" for such dispute resolution.[45] The SDR-SMG's requirements for resolving scientific disputes at the Center-level begin with an obligation on the part of Center management to ensure open scientific debate on controversial issues:

> Center management shall create an atmosphere in which consultation and open discussion on controversial issues are encouraged. When disagreements occur, it is necessary to follow appropriate procedures for resolving them. Informal methods, using good management practices for resolving conflict, should be employed prior to instituting the more formal procedures described here. Notwithstanding informal good management practices used to try to resolve the conflict, timely written reviews of the scientific matter in dispute should be completed by all members of a review group, including initiator and supervisors, to enable as open and complete a discussion of the issues as possible at the working level of the organization.[46]

The SDR-SMG then goes on to require the Centers to have in place written standard operating procedures for formally resolving scientific disputes (SDR-SOPs) in the event that such informal attempts at resolution are unsuccessful.[47] In contrast to the procedural review contemplated by

[40] 79 Fed. Reg. 65410, 65411 (Nov. 4, 2014).
[41] SDR-SMG at 1.
[42] *Id.* at 2.
[43] *Id.* at 12.
[44] *Id.* at 12-13.
[45] *Id.* at 2-3.
[46] *Id.*at 6.
[47] *Id*.

the SDR-SMG, Center-level SDR-SOPs should provide for substantive review of the scientific disputes at issue within the Center.[48]

At CDER, there are three interrelated chapters of the Center's Manual of Policies and Procedures (MAPPs) that serve to implement the SDR-SMG's requirements. The first, MAPP 4151.8, "Equal Voice: Discipline and Organizational Component Collaboration in Scientific and/or Regulatory Decisions," sets forth CDER's principles for resolving scientific disputes informally and requires "a collaborative environment for decision-making."[49] According to the MAPP, "[s]uch an environment requires open communication and exchange of ideas in a mutually respectful professional environment[] and the full and open participation of all relevant disciplines and organizational components in the decision-making process."[50] MAPP 4151.8 states that "[e]ach individual who contributes to the decision-making process" must "be sure the position represented is consistent with the scientific, regulatory, and/or administrative policies of that . . . organizational component" and that "[o]pinions of staff should be documented and supported by data in a matter commensurate with the magnitude of the decision being made."[51]

The second and third MAPPs at issue directly relate to CDER's formal SDR process. MAPP 4151.1, "Scientific/Regulatory Dispute Resolution for Individuals Within a Management Chain," provides for raising a scientific issue to the "Next Highest Management Official" (NHMO) if alignment on an issue cannot be reached by the staff on a team or through discussions with a team leader or first-level supervisor. The individual who disagrees with the decision (the disputant) ". . . may initiate a dispute resolution process by writing a statement (called a dispute statement) describing the position, concept, opinion, or recommendations with which the disputant disagrees . . . as well as the proposed changes and rationale for the changes in recommendations and/or conclusions."[52]

The disputant submits the statement to the NHMO, i.e., "the management official one level above the management official who made the decision being disputed."[53] The NHMO then issues a written decision on the issue, and any disputant may then appeal the written decision up the chain of command all the way to the Center Director through use of the same process.[54] MAPP 4151.2, "Resolution of Differing Professional Opinions: Review by Ad Hoc Panel and CDER Director," provides for further formal review under certain circumstances if alignment cannot be reached under the process in MAPP 4151.1.[55] A CDER employee may initiate the process by submitting a written package, which must include "[a]n assessment of the possible significant negative consequences to the public health" at issue in the dispute, to the CDER Ombudsman.[56] The CDER Ombudsman and the Center Director then "determine whether the consequences of the decision in question are potentially serious enough to warrant" additional review.[57] If so, the Center Director appoints a chairperson to lead an *Ad Hoc* review panel for purposes of evaluating the scientific dispute and providing a recommendation to the Center

[48] *See id.*; *see also* footnote 136.
[49] MAPP 4151.8 at 2.
[50] *Id.*
[51] *Id.* at 2-3.
[52] MAPP 4151.1 at 3.
[53] *Id.*
[54] *Id.* at 4.
[55] *Id.* at 5; MAPP 4151.2 at 1-2.
[56] MAPP 4151.2 at 5.
[57] *Id.*; *see also id.* ("In most cases, the Ombudsman will ensure that all other avenues for resolution (e.g., dispute resolution process, Advisory Committee discussion, CDER regulatory briefing) have been exhausted . . . .).

Director, who renders the final decision.[58] The *Ad Hoc* panel typically includes one member with relevant technical expertise, one member chosen from a list provided by the person requesting review, and, if possible, one member with relevant expertise who is external to the agency.[59]

4. Procedural History of the Dispute in CDER

Sarepta submitted its NDA for eteplirsen (#206488) on June 26, 2015.[60] CDER assigned it for review to the Division of Neurology Products (DNP) within ODE-I, the office for which Dr. Unger serves as Director.[61] Even before submission of the NDA, however, representatives from the Office of New Drugs (OND), DNP and ODE-I (the review team) regularly briefed Dr. Woodcock on issues related to the ongoing study of eteplirsen pursuant to an investigational new drug application (IND) and the anticipated NDA.[62] The discussions at these briefings included among their topics: the suitability of eteplirsen for accelerated approval, an overview and background for eteplirsen, study design, a clinical site inspection report for Sarepta, general brainstorming, and planned communications.[63] Dr. Unger told the SDR Board both that there were far more briefings of the Center Director than is typical and that the scope of those briefings included an unusual level of detailed discussion.

During the SDR Board's separate interviews of Dr. Unger and the review team member (RTM), the SDR Board learned that, at Dr. Woodcock's direction, the review team also joined her in meetings with patient advocacy groups for DMD on multiple occasions—anywhere from six to twelve times—from very early on in the review process. The RTM described the meetings with the patient advocacy groups, which frequently included boys with DMD and their parents, as "intense," "personal," and "intimidating." Dr. Unger and the RTM both thought that Dr. Woodcock's early interest and involvement in DNP's approach to guiding the development of eteplirsen was based in part on the enthusiasm in the DMD community in relation to an article published about the initial findings for Study 201/202, which Drs. Unger and Woodcock now agree are misleading and unreliable. Indeed, Dr. Woodcock told the SDR Board that she became involved because of the broader public interest the article generated, along with encouragement from the Commissioner of Food and Drugs at the time and her long-held belief that OND has been very conservative in evaluating drugs for accelerated approval. In his decisional memorandum, Dr. Unger explains the excitement surrounding eteplirsen at the time as follows:

> [The initial findings for Study 201/202] were substantially reported in a 2013 publication, which claimed that eteplirsen markedly increased functional dystrophin production: "*…the percentage of dystrophin-positive fibers was increased to 23% of normal; no increases were detected in placebo-treated patients (p≤0.002). Even greater increases occurred at week 48 (52% and 43%*

[58] *Id.* at 6-7.
[59] *Id.* at 6.
[60] Unger Decisional Memorandum at 1.
[61] *Id.* at 2.
[62] Appeal at 24-25; Chronology prepared by Virginia Behr and submitted to the SDR Board (Behr Chronology) at 1-2. In his appeal, Dr. Unger consistently refers to the representatives from OND, OND-I and DNP who were involved in the review of the eteplirsen NDA as the "review team" or as "the division," even though he appears to be referring to senior management within OND on occasion. Dr. Woodcock has also used the same terminology on occasion, though not as consistently. For the sake of efficiency, this memorandum refers to everyone at CDER who was involved in the review of the eteplirsen NDA, besides Dr. Woodcock herself, as the review team. Nonetheless, the SDR Board notes that, within FDA, "review team" is often used to reflect the core team of individuals within a division who are directly engaged in the review of the science underlying a regulatory submission.
[63] Appeal at 24-25; Behr Chronology at 1-2.

in the 30 and 50 mg/kg cohorts, respectively), suggesting that dystrophin increases with longer treatment. Restoration of functional dystrophin was confirmed by detection of sarcoglycans and neuronal nitric oxide synthase at the sarcolemma." The publication also stated that dystrophin expression was confirmed by Western blot, with a figure showing what were termed "representative" results.

Publication of this paper was followed by a Sarepta press release, which also claimed a remarkable treatment effect from eteplirsen and raised wildly unrealistic expectations in the DMD community.[64]

In their interviews with the SDR Board, Dr. Unger and Dr. Woodcock stated that FDA also received significant correspondence from the public and Congress, much of which urged approval of eteplirsen.[65] Some of the correspondence used vulgar language and was abusive to the review staff.[66]

The briefings of Dr. Woodcock began again five to six months after submission of the NDA for eteplirsen.[67] The focus of these briefings was on preparation for a planned meeting of the Peripheral and Central Nervous System Drugs Advisory Committee (AC meeting) to provide advice on the review of the eteplirsen NDA, which meeting was initially scheduled for January 2016 but then rescheduled for April 25, 2016.[68] The preparation involved discussions of the ongoing review of the data, including the "strengths, limitations, and uncertainties of the data, particularly with respect to the comparison between the open-label eteplirsen group and a contemporary untreated external control group."[69] During their respective interviews with the SDR Board, both Dr. Unger and the RTM conveyed their belief that Dr. Woodcock was inclined to grant approval from very early on in the process. But the RTM stated that Dr. Woodcock's views were not always clear during discussions throughout the review of the science—sometimes she seemed to agree with external constituents, sometimes not. The RTM told the SDR Board that, in his or her view, the review team was never sure whether they were discussing science, policies, or politics. According to both Dr. Unger and the RTM, Dr. Woodcock frequently conveyed that she thought the review team was being unreasonable and encouraged DNP to find a way to approve the eteplirsen NDA. Both Dr. Unger and the RTM told the SDR Board that Dr. Woodcock seemed focused on the external pressures, from both patient advocacy groups and Congress, and that she frequently talked about the effects of a decision regarding eteplirsen in terms of overarching policy (e.g., the need to be more flexible for ultra-rare diseases). The RTM highlighted to the SDR Board that at least two members of the review team were leaving FDA or had left the agency in the wake of both the decision-making process within CDER and the pressures exerted by outside forces.

Dr. Woodcock conceded to the SDR Board that she was leaning toward granting approval in light of the available data as early as 2014. She said that her goal throughout the discussions

[64] Unger Decisional Memorandum at 11 (emphasis in original), citing Mendell JR, *et al*: Eteplirsen for the treatment of Duchenne muscular dystrophy. *Ann Neurol* 2013;74:637-47 and Sarepta press release, dated 8/8/13 (http://investorrelations.sarepta.com/phoenix.zhtml?c=64231&p=irolnewsArticle&ID=1846052). Dr. Unger also notes, "It was these perceptions and expectations that led the applicant to declare that a placebo-controlled study was no longer feasible." Unger Decisional Memorandum at 11.
[65] *See also* Appeal at 23.
[66] *See, e.g., id.* at 23-24.
[67] *Id.* at 25; Behr Chronology at 2-3.
[68] Appeal at 25; Behr Chronology at 2-3.
[69] Appeal at 25.

with the review team was to convince them to come around to her more flexible way of thinking about the data. According to Dr. Woodcock, she recognized that there were serious and significant flaws in the study design for Study 201/202 and the data it generated but that she did not "want to hold" those flaws "against the patients." She conceded that the results produced by Studies 201/202 and 301 were always less than anyone in CDER had hoped.

In their respective interviews with the SDR Board, both Dr. Unger and the RTM focused to some extent on Dr. Woodcock's involvement in the planning stages for the AC meeting. They expressed some surprise at the extent of her involvement. Dr. Unger indicated in his interview with the SDR Board that Dr. Woodcock even advocated, unsuccessfully, for changing the order of the questions to be posed to the committee and wanted the question on conventional approval to come before the one on accelerated approval.

The RTM told the SDR Board: (1) that Dr. Woodcock made it clear in one or more of the meetings leading up to the AC meeting that she intended to speak at the meeting but (2) that the substance and purpose of her participation were never communicated. Although the RTM affirmatively stated that the review team was free to develop its own presentation to the committee, uncertainty with respect to Dr. Woodcock's role made doing so more difficult. The RTM also noted that Dr. Woodcock requested a longer than is typical Open Public Hearing portion of the AC meeting that, as a result, the review team thought there would insufficient time for them to make their presentations during a one-day meeting. The RTM stated that the review team asked to extend the advisory committee to two days but that they were overruled.

On April 25, 2016, CDER held the AC meeting. The meeting focused on the data from Study 201/202.[70] Dr. Woodcock spoke at the meeting several times. At the meeting she made a presentation that was intended to "provide a framework within which to consider [the] data [underlying the eteplirsen NDA] based on [her] 30 years of experience at FDA and really extensive experience in implementation of the legal standards for drug approval."[71] She highlighted many of the difficulties in interpreting the data.[72]

At the AC meeting, Dr. Woodcock also described the standards for both conventional and accelerated approval of drugs but mentioned that the agency had not "articulated an evidentiary standard for determining if a surrogate endpoint is reasonably likely to predict clinical benefit."[73] She concluded her presentation with the following remarks:

> I would note that much of the effort in evaluating a drug development program goes into avoiding a specific mistake, that is erroneously approving a drug that is not effective.
>
> There often is little consideration of another error, which is failing to approve a drug that actually works. In devastating diseases, the consequences of this mistake can be extreme, but most of these consequences are borne by patients who traditionally [] have little say in how the standards are implemented.
>
> The accelerated approval program includes a requirement for confirmatory studies for efficacy, so as you've heard from the sponsor, you have to do further studies to explore and confirm effectiveness. An inherent

[70] Sarepta had not yet submitted the data from Study 301.
[71] Advisory Committee Transcript at 151.
[72] *Id.* at 151-155.
[73] *Id.* at 155-156.

> presumption in this program of accelerated approval, which is written in the preamble to our regulation about it, is that more uncertainty is going to be tolerated initially and that in fact sometimes we will collectively get it wrong, otherwise accelerated approval would really have no different standards than regular approval.[74]

During the questions to the committee members, Dr. Woodcock restated the standard for accelerated approval and emphasized that, with regard to the surrogate endpoint of dystrophin, there has never been a "threshold established [to show a reasonable likelihood of predicting clinical benefit] because there's never been a drug to do this."[75] When later asked for clarification of the extent to which the committee members were to incorporate the testimony of the boys and their families into their evaluation of clinical outcomes for Study 201/202, Dr. Woodcock stated:

> Well, we are instructed, as people said, to take the use of the patient community into account, more on the benefit and the risk. * * * So the statutory standard is more or less as described there, but there is flexibility, and that's where we should take the views of the community into account.[76]

During his SDR Board interview, the RTM stated that, notwithstanding Dr. Woodcock's emphasis on accelerated approval and the standard of "reasonably likely to predict clinical benefit," "[s]urrogacy was not discussed in any genuine scientific way" during the AC meeting because it had not been framed that way by Sarepta through its presentation to the committee. The RTM specifically stated that there was no discussion of "substantial evidence" in the context of accelerated approval, nor what might constitute "interpretable evidence." The RTM believed that, by the end of an emotional AC meeting, the framework for evaluating the data under the appropriate regulatory standards, as provided by the review team toward the start of the meeting, had been forgotten by the committee members.

Dr. Woodcock explained to the SDR Board that she thought both that the review team did a poor job framing the issues during their presentations and that the questions were confusing and poorly worded. Indeed, during her interview with the SDR Board, Dr. Woodcock opined that the review team "did not put its best foot forward." She speculated that the confounding factor was the number of interested persons attending both in person and by webcast. She stated that she did not interfere with either aspect of the AC meeting because she knew she disagreed with the review team and Dr. Unger had already signaled that he would file an SDR appeal if she decided to grant accelerated approval to eteplirsen. She thought that the review team's presentation of the IHC data, in particular, was confusing. She further opined that the review team's failure to highlight the clinical data made the questions on conventional approval and accelerated approval difficult for the committee members to understand. Dr. Woodcock also criticized the review team for how it downplayed and undercut the views of the patient advocates.

At the conclusion of the AC meeting, the committee voted against accelerated approval by a margin of 7-6.[77] Three of the members who voted in favor of accelerated approval were the consumer representative and the two patient representatives.[78]

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[74] *Id.* at 158-59.
[75] *Id.* at 484.
[76] *Id.* at 548-549.
[77] *Id.* at 486-95.
[78] *Id.* at 2-7, 486-88.

On May 4, 2016, Dr. Woodcock met with the review team to discuss the AC meeting and plan of actions for the NDA.[79] In his appeal, Dr. Unger contends that Dr. Woodcock "made clear her intent to approve the drug" at this meeting, even though she had not yet reviewed drafts of DNP's final review memorandum or his review memorandum.[80] According to Dr. Unger, Dr. Woodcock explained that she had already "reached a different conclusion" than the review team.[81] Dr. Woodcock explained to the SDR Board that the memoranda were discussed during the Center Director briefings and that she felt she understood the views of the review team and did not see the point of an "exchange of reviews."

On May 24, 2016, Dr. Unger met privately with Dr. Woodcock to discuss the eteplirsen decision.[82] On May 31, 2016, Dr. Woodcock met with representatives from the review team to discuss their reviews and her initial draft of a decisional memorandum based primarily on the data from Study 201/202.[83] Dr. Woodcock received comments back from the review team at the same meeting.[84] Dr. Unger told the SDR Board that he and members of the review team—including Dr. Robert Temple, Deputy Center Director for Clinical Science and Dr. John Jenkins, Director of OND—discouraged Dr. Woodcock from finalizing the decisional memorandum and granting accelerated approval for eteplirsen until the additional data from Study 301 could be obtained.

On June 3, 2016, in response to an email from Sarepta, a letter signed by Dr. Woodcock issued to the sponsor.[85] The letter requested the additional data from Study 301, which was to include comparisons of any biopsy samples obtained at Week 48 to the respective baseline samples for those patients.[86] The letter stated,

> If you are successful in showing, to FDA's satisfaction, a meaningful increase in dystrophin by Western blot analysis between the paired pre-and post-treatment samples, we expect to be able to grant an accelerated approval within four business days of receiving the data (assuming all other aspects of the application are approvable).[87]

Dr. Woodcock explained that Dr. Unger and the review team essentially agreed to the timeframe of four business days, though they pushed instead for six. She felt that there was general agreement that data from only twelve patients could be reviewed quickly, especially given that representatives from CDER would be overseeing the Western blot analysis and ensuring that it was done properly.

On June 27, 2016, Sarepta submitted the requested data.[88] Dr. Woodcock explained that accelerated approval was not granted within four business days of that date precisely because the results of the analysis were disappointing in that they provided evidence of only a minimal increase in dystrophin at 48 weeks. Dr. Unger sent an email to Dr. Woodcock that read:

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[79] Appeal at 25; Behr Chronology at 2.
[80] Appeal at 26.
[81] *Id.*
[82] Behr Chronology at 2.
[83] Appeal at 26; Behr Chronology at 2.
[84] Behr Chronology at 2.
[85] June 3, 2016, General Advice letter.
[86] *Id.* at 1.
[87] *Id.* at 1-2.
[88] Unger email to the SDR Board, dated July 22, 2016.

> I don't have to tell you how difficult the eteplirsen decision has been for many of us in ODE-I. As you know, we have reached different scientific conclusions on the strength of the data, and in particular, the likelihood that the small increase observed in Becker-type dystrophin is reasonably likely to predict clinical benefit. This decision could be precedent setting with respect to accelerated approval, i.e., where the bar should be set for changes in a pharmacodynamic biomarker that are deemed "reasonably likely to predict clinical benefit." Moreover, to my knowledge, this could be the first time a Center Director has overruled a review team (and an advisory committee) on a question of whether effectiveness has been demonstrated.
>
> I know that Dr. Jenkins has mentioned the possibility of involving Dr. Califf in the eteplirsen decision on at least one occasion, and I would like to request a formal appeal to the Commissioner on this matter.
>
> I'm aware that the Commissioner's official role is to consider the administrative aspects of review decisions and not the science. But given the potential for setting a precedent here, I think he should be aware of the various points of view and consider the potential ramifications of the matter at hand.
>
> I'm also aware that you advised Sarepta that we would be prepared to grant accelerated approval of their NDA within 4 business days of receiving their new data, but there was a provision in the letter that the increase in dystrophin had to be meaningful, and we do not have agreement on this point. Thus, it is my hope that a Commissioner Briefing can be held before an action is taken.
>
> I have discussed the above with Dr. Jenkins, and he supports this course of action.
>
> I propose that we reserve a few minutes at the briefing tomorrow to discuss this matter.[89]

On July 6, 2016, Dr. Woodcock met with the review team one final time.[90] During the meeting, Dr. Woodcock "indicated to the review team that [she] had read their memoranda that had been updated to reflect the new [Western blot] data, and that [she] maintained [her] position that the application should receive accelerated approval based on dystrophin production."[91] She discussed her rationale, which—based on her notes—appears to have tracked the rationale in her final decisional memorandum.[92]

On July 8, 2016, in light of Dr. Unger's stated intention of filing an appeal with the Office of the Commissioner, Virginia Behr, CDER Ombudsman, began working with him and Dr. Woodcock to determine whether the institution of any formal appeals under CDER's SDR-SOPs was warranted.[93] Ms. Behr had determined that the procedure outlined in MAPP 4151.1,

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[89] Unger email dated July 5, 2016.
[90] Appeal at 26; Behr Chronology at 3.
[91] Woodcock's handwritten notes, dated July 6, 2016, at 1.
[92] *Id.* at 2. Also of note, on July 7, 2016, Dr. Unger briefed you on his rationale for disagreeing with Dr. Woodcock's underlying scientific reasoning for granting accelerated approval for eteplirsen (Behr Chronology at 3).
[93] *See* "Agreement to utilize FDA Staff Manual Guide 9010.1 for internal appeal related to NDA 206488, eteplirsen injection" (SDR-SOPs Agreement).

"Scientific/Regulatory Dispute Resolution for Individuals Within a Management Chain" did not apply because the disagreement was between the Center Director and a subordinate two levels below her.[94] She also questioned the utility of using MAPP 4151.2, "Resolution of Differing Professional Opinions: Review by Ad Hoc Panel and CDER Director."[95] She reasoned that "the CDER Director ha[d] already fully evaluated the issues and [was] one of the parties involved in the dispute" and that "utilizing this MAPP could potentially extend this already lengthy NDA action another 50 business days."[96] She nonetheless consulted with both Drs. Unger and Woodcock, who both agreed to bypass the *Ad Hoc* panel process in favor of the process outlined in the SDR-SMG.[97] During his presentation to the SDR Board, Dr. Unger also indicated that he thinks referring the matter to an *Ad Hoc* panel would have been pointless because Dr. Woodcock had already made up her mind and a new process would not have changed the outcome.

On July 11, 2016, Dr. Woodcock provided a draft of her final decisional memorandum to the review team.[98] She received comments back from Dr. Unger; Dr. Jenkins, the Director of OND; and Dr. Ashutosh Rao, of the Office of Biotechnology Products, who was also on the review team.[99] The comments from Drs. Unger and Rao do not debate the action proposed in Dr. Woodcock's draft decisional memorandum or its underlying scientific conclusions.[100] Instead, they focus on clarifying certain facts asserted in the memorandum, and Dr. Unger provided information regarding the clinical course of 11 patients enrolled in Study 201/202 to 240 weeks.[101] Dr. Jenkins provided more detailed analysis on and critique of some of Dr. Woodcock's findings and he expressed concern about her conclusions. However, he made no attempt in his written comments to dissuade her from her ultimate conclusion regarding accelerated approval.[102] By email on the afternoon of July 13, Dr. Unger stated, "I've canvassed the Division, and we have no additional comments."[103] Dr. Unger told the SDR Board that he and the review team understood that Dr. Woodcock had already made up her mind and that thus they did not see a point in criticizing Dr. Woodcock's draft decisional memorandum.

Furthermore, the RTM told the SDR Board that some of the positions taken by Dr. Woodcock in the draft decisional memorandum were brand new to him but that he did not feel any feedback he could provide would receive due consideration by Dr. Woodcock. The RTM expressed concern that Dr. Woodcock's analysis for "reasonably likely to predict clinical benefit" raised new issues and information that should have been presented at the beginning of the review and that had not been addressed by the review team or, perhaps more importantly, presented by the sponsor in support of the NDA. The RTM specifically discussed with the SDR Board the section of the finalized version of the memorandum addressing whether the data for eteplirsen is adequate to show a reasonable likelihood of predicting clinical benefit.[104] As an example of his concerns, the RTM pointed to section (B)(5) of the decisional memorandum, which details the findings in the

[94] *Id.* at 1. It is also clear from the record before the SDR Board that the supervisor between Drs. Unger and Woodcock, Dr. John Jenkins, agreed with Dr. Unger.
[95] *Id.*
[96] *Id.* at 2.
[97] *Id.*
[98] Behr Chronology at 3.
[99] Unger emails dated July 13, 2016 and sent at 12:57 AM, 9:26 AM (including attachments), and 11:19 AM (including attachment); Jenkins email dated July 12, 2016; and emails (including attachments) from Rao dated July 12 and 13, 2016.
[100] Unger emails dated July 13, 2016 and sent at 12:57 AM, 9:26 AM (including attachments), and 11:19 AM (including attachment); emails (including attachments) from Rao dated July 12 and 13, 2016.
[101] Unger emails dated July 13, 2016 and sent at 12:57 AM, 9:26 AM (including attachments), and 11:19 AM (including attachment); emails (including attachments) from Rao dated July 12 and 13, 2016.
[102] Jenkins email dated July 12, 2016.
[103] Unger email dated July 13, 2016 and sent at 3:19 PM.
[104] Woodcock Decisional Memorandum at 5-10.

scientific literature regarding "the relationship of dystrophin expression to clinical status."[105] The RTM indicated that he or she knows the scientific literature at issue very well and that he or she could have provided significant input into the evaluation of the literature and the underlying data and analysis. The RTM conveyed that he did not do so because he felt Dr. Woodcock had already made her decision.

On July 14, 2016, Dr. Woodcock finalized her decisional memorandum. She explained to the SDR Board that her conclusion regarding whether the increase in dystrophin production identified by Studies 202 and 301 was reasonably likely to predict clinical benefit was based on her own "medical/scientific judgment." She emphasized that she has thirty years of experience at FDA and that she has far more experience in assessing this type of evidence for an "ultra-rare rare" disease than the review team. She thought that the review team was unreasonable in its position on a threshold for predicting clinical benefit in this case. Her stated goal for the decisional process was to move the review team toward what she viewed as a more reasonable approach. She acknowledged that there were clear weaknesses in the data but that accelerated approval should not be limited to "sure bet" drugs and that confirmatory trials are required for a reason. Dr. Woodcock emphasized her view that the agency needs to accept more uncertainty when granting accelerated approval. She also criticized OND for not issuing clear guidance on what constitutes a sufficient drug effect to be "reasonably likely to predict clinical benefit," as she had suggested for an extended period of time. She also thought that the review team's views on balancing the mean results of a clinical study with a targeted evaluation of responsive patients were misplaced, particularly in a DMD population, where additional genetic mutations or deficiencies could have a profound effect on the outcome.

In her presentation to the SDR Board, Dr. Woodcock suggested that, in making the decision, she was looking at the broader picture for the development of these types of drugs for very limited patient populations in the United States (between 600 and 1300) and that there needed to be some path forward for such innovative products. She opined that Sarepta in particular "needed to be capitalized." She noted that the sponsor's stock went down after the AC meeting and went up after FDA sent the June 3, 2016 letter. Dr. Woodcock cautioned that, if Sarepta did not receive accelerated approval for eteplirsen, it would have insufficient funding to continue to study eteplirsen and the other similar drugs in its pipeline. She stated that, without an approval in cases such as eteplirsen, patients would abandon all hope of approval for these types of products and would "lapse into a position of" self-treatment.

On July 16, 2016, Dr. Unger finalized his own decisional memorandum. In her own decisional memorandum, dated July 14, 2016, Dr. Woodcock indicated that she had read Dr. Unger's decisional memorandum,[106] although she could not have done so given the timing of the two memoranda. She explained to the SDR Board that she did not feel she needed to see a finalized version of Dr. Unger's decisional memorandum because she was already familiar with his views on the data and the decision. She also stated that there was nothing in Dr. Unger's appeal, which is based largely on his finalized decisional memorandum, that would have changed her mind on her decision or the underlying rationale. She stated, "He is entitled to his own opinion."

5. Dr. Unger's SDR Appeal

In his appeal, Dr. Unger focuses his arguments almost exclusively on the substance of his scientific disagreement with Dr. Woodcock. Indeed, Dr. Unger makes clear in his appeal that he

[105] *Id.* at 7-10.
[106] *Id.* at 1.

seeks "a scientific review on the matter of whether or not there is substantial evidence of a quantitative effect on dystrophin protein that is reasonably likely to predict clinical benefit."[107] Insofar as he explicitly addresses potential procedural issues under the review process contemplated by the SDR-SMG, he does so in two paragraphs toward the end of the appeal.[108] He first states that Dr. Woodcock's "direct involvement with this drug, compared to other development programs, has been unprecedented."[109] He states further that "[s]he also attended the April meeting of the Peripheral and Central Nervous System Drugs Advisory Committee, where she spoke and interjected a number of important comments."[110] After conceding that "[t]here is no question that there has been adequate time and place for the discussion of various views," Dr. Unger notes that he found it unfortunate that "the Center Director made clear her intent to approve the drug at a briefing with the review team on May 4, 2016, before she had seen drafts of the Division's final review memorandum or my review memorandum."[111] As noted above, Dr. Unger indicates that Dr. Woodcock conveyed that she had "already '. . . reached a different conclusion . . .' than the review team."[112]

In his presentation to the SDR Board, Dr. Unger highlighted that Dr. Woodcock had never seen the charts on page 10 of his appeal. Those charts show: (1) a comparison of the *original* IHC results for baseline samples in the three patients whose biopsies were available at 180 weeks to the IHC results for those same samples when they were re-evaluated after 180 weeks and (2) a comparison of the IHC and the Western blot results at 180 weeks.[113] Dr. Unger stated, however, that those charts were consistent with his earlier positions and would likely not affect Dr. Woodcock's analysis or decision. In a follow-up email to the SDR Board, Dr. Unger also contended that Dr. Woodcock diverted from protocol when she finalized her decisional memorandum on July 14, 2016, two days before his.

In his appeal, Dr. Unger frames his scientific disagreement with Dr. Woodcock as follows: "The disagreement is over the question of whether the findings on the dystrophin surrogate endpoint are reasonably likely to predict clinical benefit."[114] Nonetheless, Dr. Unger explains his disagreement with Dr. Woodcock through multiple challenges to the reliability of the underlying data and specific issues he has with her rationale or the evidentiary basis for such rationale. Of note, he makes the following scientific arguments:

- As noted above, Study 201 showed only "a nominally statistically significant increase in dystrophin in response to eteplirsen for the low dose group…";[115]
- Study 201/202 was fundamentally flawed in several respects:
  - "[T]he baseline biopsies were obtained from [external controls] . . . who could differ in unknown ways from the subjects in Study 201/202";[116]
  - "[T]he Week 180 biopsies were obtained from different muscles than the baseline biopsies";[117] and

[107] Appeal at 26.
[108] *Id.*
[109] *Id.*
[110] *Id.*
[111] *Id.*
[112] *Id.*
[113] *Id.* at 10.
[114] *Id.* at 3.
[115] *Id.* at 9.
[116] *Id.* at 5.
[117] *Id.*

- "The baseline biopsies for the three subjects with Week 180 data had been stored for several years and the protein may have degraded, leading to a falsely low baseline value, and a greater apparent increase from baseline…."[118]

- Although the available data generated by Study 301 were the product of an adequate and well-controlled study and showed a statistically significant increase of dystrophin, the drug effect (i.e., an increase from 0.22% to 0.32% of normal) is not reasonably likely to predict clinical benefit.[119]
  - "The treatment effect observed cannot be compared or related to levels of dystrophin measured by other laboratories and reported in various publications";[120]
  - "Dr. Woodcock never provides a rational argument – based on reliable data – to support the concept that '…low-level increases in dystrophin production are reasonably likely to predict clinical benefit.' She provides no rationale – no link between a mean increase in dystrophin of 3 parts per thousand and clinical benefit";[121] and
  - "No evidence of a clinical effect was demonstrated in the eteplirsen development program, and there is no correlation between dystrophin levels as determined by Western blot and clinical outcome."[122]

He also makes several overarching policy and legal arguments that call into question the appropriateness of Dr. Woodcock's decisional memorandum. His key arguments focus on the effects that Dr. Woodcock's decision would have on the pathway for accelerated approval and the standard for "reasonably likely to predict clinical benefit."[123] He also highlights the negative effects that accelerated approval would have on the patients themselves, including false hope, abandonment of other therapies, and a decline in drug development for DMD.[124] He further questions "the ethics of approving or prescribing a drug for a fatal disease at a dose that is very likely to be sub-therapeutic[] when the consequence of a sub-therapeutic dose is clinical deterioration and death."[125] Finally he worries that approving eteplirsen based on the data submitted by the sponsor "would send the signal that political pressure and even intimidation—not science—guide[] FDA decisions."[126]

ANALYSIS

1. Whether CDER followed its own processes.

The first issue for the SDR Board to consider is whether CDER followed its own processes in addressing Dr. Unger's scientific dispute. Dr. Unger does not contend that there were any issues with respect to how CDER chose to address and implement its own formal appeals process under the SDR-SOPs in this case. In his appeal, Dr. Unger points instead to four deviations from typical Center process: (1) Dr. Woodcock's involvement in the early stages of review of the eteplirsen NDA; (2) her extensive involvement in planning the AC meeting and her participation

[118] *Id.*
[119] *Id.* at 7.
[120] *Id.* at 13.
[121] *Id.* at 15.
[122] *Id.*
[123] *Id.* at 21-22.
[124] *Id.*
[125] *Id.* at 23; *see also* Unger Review Memorandum at 4, 5.
[126] *Id.*

in the meeting; (3) her initial decision (on May 4, 2016) to approve the eteplirsen NDA before the review team had completed even their draft review memoranda; and (4) her issuance of her final decisional memorandum before Dr. Unger finalized his own decisional memorandum as Director of ODE-I. In its review of the administrative file and the surrounding circumstances, the SDR Board has also identified below other potential deviations from process at the Center level.

The agency-wide SDR-SMG directs the SDR Board to focus on the Center's SDR-SOPs in evaluating whether the Center followed its own processes in evaluating a scientific dispute. In this case, however, both Drs. Unger and Woodcock have agreed that the only applicable SDR-SOP, MAPP 4151.2, provides for a review by the Center Director in consultation with an *Ad Hoc* panel and that going through such a process at this stage would be futile. The SDR Board has determined that, absent the second aspect of that agreement regarding futility and the underlying unusual circumstance of this scientific dispute, there would be reason to refer the matter back to the Center for further review by an *Ad Hoc* panel.

The interplay between MAPP 4151.1 and 4151.2, the former of which provides for supervisory review of scientific disputes all the way to the Center Director, suggests that MAPP 4151.2 actually calls for additional review of a scientific dispute by the Center Director under certain circumstances even if she has already made a decision on the dispute. Although MAPP 4151.2 provides for bypassing review of the scientific dispute up the chain of command under MAPP 4151.1 if such exhaustion would impede the timely resolution of a serious public health issue, MAPP 4151.2 also emphasizes that it should not be used before other means of resolution have been attempted.[127] However, the key consideration for obtaining review by an *Ad Hoc* panel under MAPP 4151.2 is "whether the consequences of the decision in question are potentially serious enough to warrant [additional review]," not whether the resort to the process would be futile.[128] It appears that Dr. Woodcock has never made a determination regarding the seriousness of the decision in question, but it would be surprising if she determined that the dispute in this case did not meet the standard, as reflected in the statement she signed.[129]

In this case, however, it is clear from the record before the SDR Board that Dr. Woodcock was so involved in the underlying scientific dispute—including direct and extensive personal review of the data and analyses offered in support of the NDA—that we agree with the conclusion in the agreements signed by Drs. Unger and Woodcock that "the CDER Director has already fully evaluated the issues."[130] Indeed, she has already received advice from an advisory committee and had substantial conversations with her staff over an extended period of time with respect to the dispute in question. There is no reason to believe that receiving additional advice from an *Ad Hoc* panel would alter Dr. Woodcock's views of the scientific issues. As the agreement between her and Dr. Unger reflects, the process would be time-consuming and delay an important

[127] MAPP 4151.2 at 5. ("In most cases, the Ombudsman will ensure that all other avenues for resolution (e.g., dispute resolution process, Advisory Committee discussion, CDER regulatory briefing) have been exhausted before a [request for review under 4151.2] is filed. However, in some cases, an individual may believe that his or her professional opinion will not be considered by his or her supervisors or that there is not time to exhaust other options for dispute resolution without seriously endangering the public health. In this case, the submitter should include . . . a written request to bypass these other mechanisms. . . .).
[128] *Id.*
[129] SDR-SOPs Agreement at 2 ("The difference of opinion between Drs. Unger and Woodcock could be considered to meet the criteria for filing an appeal under MAPP 4151.2 because the drug indication sought is one for a serious and life-threatening disease that has limited treatment options.").
[130] *Id.*

regulatory decision unnecessarily.[131] Dr. Unger also told the SDR Board that he thought going through the *Ad Hoc* panel process would have been pointless for the aforementioned reasons.

The difficulty for the SDR Board is that the agency-wide SDR-SMG is predicated on some level of formal scientific dispute resolution within the Center, particularly a decision by the Center Director regarding the formalized scientific dispute.[132] For that reason, the focus of the SDR-SMG with respect to the process followed is on whether the Center followed its own SDR-SOPs in resolving the scientific dispute.[133] Yet, the SDR-SMG also directs the Centers to adopt "[i]nformal methods" for resolving scientific disputes, "to create an atmosphere in which consultation and open discussion on controversial issues are encouraged," to use "good management practices for resolving conflict," and "to enable as open and complete a discussion of the issues as possible at the working level of the organization."[134] As a result, the SDR Board has determined that reviewing the processes used by a Center to resolve a scientific disagreement is appropriate under the SDR-SMG even when, as here, the initiator has not availed himself of the Center's formal process for resolving scientific disputes and the Center Director has explicitly agreed to that approach.

Whether the Center followed its own processes for resolving a scientific disagreement cannot be viewed in a vacuum, however. Indeed, the SDR-SMG itself—at its most concise and in its clearest voice—states, "The goal of [the SDR Board's] review is to determine if the processes followed in the Center fully considered all relevant evidence and provided the initiator with an opportunity to express his or her concerns at all appropriate levels, prior to and including the Center Director."[135] Particularly in the context of a scientific dispute that did not go through a formal SDR process at the Center but nonetheless received extensive review by the Center Director, focusing on deviations from process without any regard to whether they affected the initiator's opportunity to present his views of the science (and to some extent whether those views and the evidence were considered) would seem to miss the point of that review. Accordingly, the SDR Board finds that it is more appropriate to address Dr. Unger's arguments regarding the Center's deviations from appropriate process under the second prong of its analysis: whether the Center provided Dr. Unger an adequate opportunity present his scientific concerns.

The SDR Board's one caveat is that, as noted above, the SDR-SMG does appear to assume that there has been both at least some use of the formal dispute resolution within the Center and, accordingly, a *formal* substantive review of the initiator's scientific concerns before reaching the Office of the Commissioner.[136] The limited scope of the SDR Board's review under the SDR-SMG—i.e., an evaluation of the Center's decision-making process—means that Dr. Unger will also not receive a substantive review of his scientific concerns under the SDR-SMG. In fact, at the conclusion of the SDR Board's review, Dr. Unger will not have received a substantive review of his scientific concerns under any formal process at any level. Particularly in light of

[131] *Id.* ("[U]tilizing this MAPP could potentially extend this already lengthy NDA action another 50 business days.").
[132] *See* SDR-SMG at 6 (requiring as a mandatory process for formal scientific dispute resolution a written opinion by the Center Director and stating that such a written opinion as a step in the process is a "central criterion for advancement to the agency-level appeals process.").
[133] *See, e.g., id.* at 12 (requiring the SDR Board to "obtain the full administrative record of the Center's processes for the dispute and review the Center's published SOP(s)" and to "review that information to determine whether written Center processes were followed.").
[134] *Id.* at 6.
[135] *Id.* at 12.
[136] *See id.* at 6 (referring to SOPs for resolution of Center-level scientific disputes without limiting them to procedural reviews and contemplating the Center SOPs as a continuation of the informal SDR process).

Dr. Unger's explicit request for scientific review of the matter within the Office of the Commissioner, therefore, the SDR Board recommends additional substantive review at this level, as is discussed below.

2. *Whether CDER provided an adequate opportunity to Dr. Unger to present his scientific concerns.*

In his appeal, Dr. Unger admits, "There is no question that there has been adequate time and place for the discussion of various views."[137] In so doing, he appears to concede away most of his arguments with respect to whether he had an adequate opportunity to present his scientific concerns, notwithstanding the procedural deviations he identifies. The SDR Board, however, has not taken Dr. Unger's concession at face value and has instead looked beyond it to evaluate the administrative file and the surrounding circumstances to identify additional procedural issues. We conclude nonetheless that Dr. Unger had an adequate opportunity to present his scientific concerns to Dr. Woodcock before she issued her decisional memorandum.

As noted above, Dr. Unger identified four deviations from Center's typical decision-making process for the eteplirsen NDA: (1) Dr. Woodcock's involvement in the early stages of review of the eteplirsen NDA; (2) her extensive involvement in planning the AC meeting and her participation in the meeting; (3) her initial decision (on May 4, 2016) to approve the eteplirsen NDA before the review team had completed even their draft review memoranda; and (4) her issuance of her final decisional memorandum before Dr. Unger finalized his own decisional memorandum as Director of ODE-I. In reviewing this matter, the SDR Board—which includes among its members Ombudsmen from other Centers that oversee reviews of medical products—also considered other departures from the typical processes used by Centers in reviewing applications for pre-market approval or clearance.[138]

The SDR Board agrees with Dr. Unger that it was unusual for a Center Director to be so involved in the early stages of reviewing an NDA, but the consensus on the SDR Board was that Dr. Woodcock went several steps further than mere involvement and thereby departed from typical practice among the Centers. By her own admission, Dr. Woodcock had a direct hand in reviewing the data submitted in support of the NDA, even before the review team had written their draft review memoranda, and actively encouraged the review team—including Dr. Unger—to come around to her way of thinking in their own reviews. Specifically, she wanted the review team to agree with her that the limited increase in dystrophin production established by the data in Studies 201/202 was sufficient to show a reasonable likelihood of predicting clinical benefit. At several points during the decision-making process for what is clearly a critical scientific issue for the agency, Dr. Woodcock also provided a very limited amount of time for Dr. Unger and the review team to provide feedback on additional data or her own scientific conclusions—most notably when Sarepta submitted the data from Study 301 and when she provided two separate draft versions of her decisional memorandum to the review team.

Notwithstanding the foregoing procedural shortcomings, the SDR Board finds that Dr. Unger had an adequate opportunity to present his scientific views. Not only does he admit in his appeal that he had an opportunity, but the record before the SDR Board demonstrates that he did. He and the rest of the review team met with Dr. Woodcock on multiple occasions both before and after the AC meeting. Drs. Unger and Woodcock both told the SDR Board that those meetings involved substantive and detailed discussions of the data and science and the appropriate

[137] Appeal at 26.
[138] *See* SDR-SMG at 3 (defining the SDR Board to include Ombudsmen from all of the Centers).

conclusions to be drawn from them. Although Dr. Unger complains that Dr. Woodcock was involved in aspects of the NDA that went far beyond the norm for a Center Director at CDER, including her role in the AC meeting, and that she reached or finalized decisions before reviewing review or decisional memoranda, he does not maintain that those procedural deficiencies compromised his ability to present his views. In fact, his own final decisional memorandum—which Dr. Woodcock apparently saw in draft form before she finalized her own—discloses that he felt empowered to push back on both Dr. Woodcock's scientific conclusions and their basis, despite the fact that he believed his efforts would be futile. Indeed, he conceded to the SDR Board that nothing in his decisional memorandum or appeal submission would have affected Dr. Woodcock's decision on the scientific issue in question (including the charts that he created for the first time in preparing his appeal submission under the agency-wide SDR-SMG). He further conceded as much when he agreed not to pursue further review through the *Ad Hoc* panel process under CDER's SDR-SOPs. In short, through his own perseverance, confidence in his own scientific expertise, and perhaps dint of personality, Dr. Unger ensured that he himself had an adequate opportunity to present his scientific views despite the procedural irregularities in the decision-making process within CDER.

The SDR Board nonetheless remains concerned about Dr. Woodcock's extensive involvement in the review of the eteplirsen NDA, including her degree of participation at the AC meeting, and the limited timeframe she provided for feedback on the data from Study 301 and her own scientific conclusions on that data. We fear that those actions could have chilled scientific debate within CDER and reduced the level of participation by the review team during the final stages of the decision-making process. By all accounts, Dr. Woodcock made clear her views that CDER should lean toward finding that eteplirsen met the standards underlying accelerated approval nearly from the outset of her involvement. By May 4, 2016, she had orally communicated her intention to grant accelerated approval for eteplirsen, even though she had not yet seen even the draft review memoranda from the review team or a decisional memorandum from Dr. Unger. Then, when she requested data from Study 301 from Sarepta, she communicated to the sponsor a compressed timeframe for CDER's review. Although she later expanded the timeframe for review when the data proved to be disappointing, she apparently analyzed the data on her own, conducted her own additional search of the scientific literature, and took only six or seven business days to orally communicate to the review team her decision to grant approval.

To complicate matters further, Dr. Woodcock subsequently circulated a draft decisional memorandum but provided only a limited amount of time for comments, even though the draft decisional memorandum was the first time some on the review team had apparently seen key elements for the basis of her decision on "reasonably likely to predict clinical benefit." The response from the review team is telling. As noted above, only Drs. Jenkins and Unger and another reviewer outside of DNP provided comments. Except for Dr. Jenkins, no one made any effort to make substantive comments beyond tips on how to make factual clarifications or to supplement her analysis with additional data. It appears that, because the review team knew Dr. Woodcock's views by then, they saw no point in providing any additional substantive review or meaningful feedback on any new issues raised by Dr. Woodcock's memorandum. Indeed, Dr. Unger and the RTM conveyed as much to the SDR Board.

There is no doubt that a Center Director should have wide latitude in leading the direction of the Center in a manner consistent with her priorities and vision. The SDR Board also believes that Center Directors have a role to play not only with respect to the resolution of scientific disputes at issue in individual applications for pre-market-authorization by FDA, as evidenced by both the SDR-SMG and CDER's own SDR-SOPs, but also with respect to the ultimate decision on

scientific issues that are not the subject of a dispute. It is also clear from Dr. Woodcock's presentation to the SDR Board that she firmly believes in the correctness of her scientific decision in this case and that her involvement in the review of the eteplirsen NDA was always motivated by the best of intentions. However, the SDR Board finds Dr. Woodcock's extensive, early involvement in the review process troubling. Indeed, her involvement here appears to have upended the typical review and decision-making process.

Rather than ensuring that the scientific reviews started at the bottom of the chain of command, Dr. Woodcock made clear from her position at the top that she was pushing for a particular outcome from the very early stages. As a consequence, the regulatory reviews did not start at the staff level with scientific reviews and then proceed through the chain of command for concurrence or non-concurrence at all appropriate levels within the management structure, as would be the typical course of decision-making for a regulatory decision grounded in science. Indeed, before the reviewers had even completed their draft scientific reviews, Dr. Woodcock had told them—on May 4, 2016—that she intended to grant accelerated approval. This sort of top-down review does not, in the SDR Board's view, "create an atmosphere in which consultation and open discussion on controversial issues are encouraged," as reflected in the SDR-SMG's requirements for resolution of scientific disagreements by the Center.[139] By the time Dr. Woodcock issued her draft decisional memorandum on what she herself acknowledged was a difficult scientific issue of incredible magnitude for the agency—i.e., whether the evidence regarding dystrophin production was reasonably likely to predict clinical benefit—the review team had decided it was pointless to challenge her ultimate conclusion or its basis.[140] Review teams should have the opportunity to conduct their reviews without preemption by the Center Director. As noted above, the SDR Board believes that Center Directors should have a role in shaping policy, expressing concerns, and resolving issues once they are ripe for their review, but we caution that care should be taken to avoid the appearance of interfering with the integrity of scientific reviews at the lower levels of a Center.

3. Whether the Center Director considered all relevant evidence bearing on the scientific question at issue.

The third issue for the SDR Board is whether CDER, including Dr. Woodcock, fully considered all relevant evidence in resolving the scientific dispute at issue, i.e., whether the evidence of eteplirsen's effect on dystrophin production is reasonably likely to predict clinical benefit. In this case, both Drs. Unger and Woodcock appear to agree that she *considered* all relevant evidence. As noted above, Dr. Unger does not believe that any additional data or evidence available to him could persuade Dr. Woodcock that she has reached the wrong scientific conclusion. For her part, Dr. Woodcock does not feel that she has disregarded any relevant evidence. Moreover, in her interview with the SDR Board, she demonstrated an awareness and command of all of the evidence weighing against the scientific decision she has made, including the arguments and analysis of the evidence presented in Dr. Unger's appeal.

Whether Dr. Woodcock has *addressed* all of the relevant evidence in her decisional memorandum is a more difficult question. In concluding that the minimal increase in dystrophin

[139] *Id.* at 6.

[140] In this regard, it is also worth noting again the language quoted above in the background section: "Each individual who contributes to the decision-making process" must "be sure the position represented is consistent with the scientific, regulatory, and/or administrative policies of that . . . organizational component" and that "[o]pinions of staff should be documented and supported by data in a matter commensurate with the magnitude of the decision being made." (MAPP 4151.8 at 2-3).

production seen in the data is reasonably likely to predict clinical benefit, Dr. Woodcock has provided a very limited rationale.

At the risk of oversimplification, Dr. Woodcock found, in essence, that the studies attempting to correlate levels of dystrophin with clinical benefit, as have been reported in the scientific literature, are unreliable in this context for variety of reasons, including: (1) the subjectivity of the clinical evaluation, (2) the difficulty in correlating IHC results with Western blot results, (3) the influence of anti-dystrophin antibodies, (4) the lack of information on dystrophin quality (as opposed to quantity) in the different studies, (5) deficiencies in Western blot techniques from earlier studies, and (6) the wide range of findings with respect to the correlation of dystrophin levels with clinical benefit.[141] She concluded, therefore, that "protein in the range between undetectable and 10% of normal is likely to be very important for clinical presentation, all other things being equal, i.e. mutation status and non-dystrophin-related factors affecting phenotype," and that the "biochemical data strongly support the idea that low-level increases in dystrophin production are reasonably likely to predict clinical benefit."[142] She then attempted to bolster that conclusion with a theory regarding the effect of exon 52 deletion and her reanalysis of the intermediate clinical outcomes for a subset of subjects in Study 201/202.[143] She further explained to the SDR Board that she was exercising her "medical/scientific judgment" in reaching the scientific conclusion that she did.

It is easy for the SDR Board to understand why Dr. Unger's appeal expressed such frustration with this explanation of Dr. Woodcock's rationale. He states:

> I believe the burden is on Dr. Woodcock to show or explain why production of a near-zero quantity of dystrophin (0.3%) is reasonably likely to predict clinical benefit, and I do not believe her July 14, 2016 memo makes this case. I believe that the available evidence leaves open the possibility that some patients could benefit from a small increase in dystrophin, but this possibility does not reach the threshold of being reasonably likely to predict a clinical benefit.[144]

Of course, *considering* the relevant evidence and *addressing* the relevant evidence in a manner satisfactory to Dr. Unger or the SDR Board are two different propositions. The SDR Board finds, based on the record before us, that Dr. Woodcock has considered all relevant evidence in reaching her scientific conclusion. Based on her own medical judgment, she simply has a difference of opinion with Dr. Unger—both with respect to the scientific conclusion and the sufficiency of the underlying rationale.

4. Whether the dispute should be remanded to the Center Director.

Inasmuch as the SDR Board has concluded that Dr. Unger had an adequate opportunity to present his scientific concerns during the decision-making process at CDER and that Dr. Woodcock considered all relevant evidence in making her decision, the SDR Board does not recommend returning this matter to the Center Director for corrective action. We also believe that, for reasons discussed above, remanding this matter to the Center Director would be futile.

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[141] Woodcock Decisional Memorandum at 5-9.
[142] *Id.* at 9.
[143] *Id.* at 10.
[144] Appeal at 20 (emphasis in original).

CONSIDERATIONS FROM THE ACTING CHIEF SCIENTIST

In my capacity as Acting Chief Scientist, I feel the responsibility to convey some comments regarding the underlying science for the decision being challenged by Dr. Unger in his appeal. I cannot begin to understand the depth of pain and suffering that patients with DMD and their families endure. As an experienced physician, I struggle to identify any other diseases associated with this degree of suffering, not only to patients but to their families. Nevertheless, my assessment is that the data presented by the sponsor to date are not adequate to support accelerated approval of eteplirsen

Studies in animals showing that eteplirsen leads to "exon 51 skipping" are an important first step in assessing whether eteplirsen might work for a subset of patients with DMD because skipping exon 51 is necessary for the production of dystrophin in these patients.[145] The next step is to assess whether eteplirsen actually leads to the production of dystrophin in patients with DMD and, if so, whether such an increase in dystrophin confers clinical benefit. Despite the promising animal studies demonstrating exon 51 skipping, both Drs. Woodcock and Unger, as well as the review team in CDER, agree that the amount of dystrophin produced in the clinical studies conducted at doses of up to 50mg/kg per week is very low. Animal data suggest that the doses studied in humans is too low; in animals, exon 51 skipping was detected in a nonlinear, dose-dependent manner (that is, higher doses led to significantly more exon 51 skipping). Specifically, with a 1-log increase in dose (from 5 to 40 mg/kg), there was little change in exon 51 skipping. With a second log increase in dose (from 40 to 320 mg/kg), however, there was more than a log increase in response. These dose-dependent responses are important because it is wholly conceivable that higher doses would lead to a much greater amount of dystrophin production, which could be important for clinical benefit. Because the drug appears to be safe, the review team recommended evaluation of much higher doses of eteplirsen, of at least 200mg/kg per week. Approving a drug at a dose that does not show a meaningful increase in dystrophin (when the drug could theoretically achieve one at higher doses) is concerning.

As for accelerated approval, the regulatory standard at issue requires a sponsor to show that the drug under review leads to an effect on the surrogate endpoint (in this case, the production of dystrophin) and that the effect is reasonably likely to predict clinical benefit (in this case, improving, or slowing down decline in, muscle function). The term "reasonably likely to predict" acknowledges the potential for doubt in the outcome of interest. Indeed, nobody knows the minimum level of dystrophin that is likely to confer clinical benefit in patients with DMD. The critical scientific and regulatory issue at stake in CDER's decision here is whether such minute amounts of dystrophin are reasonably likely to predict clinical benefit at the dosage of the drug subject to approval. In this case, both Drs. Woodcock and Unger have attempted to provide a rationale, based on scientific and professional judgment, for whether or not such small levels of dystrophin are reasonably likely to predict the clinical effect of interest. By any meaningful objective standard, however, the overall evidence derived from eteplirsen's limited clinical development program does not support that the levels of dystrophin produced by eteplirsen at the doses studied are reasonably likely to provide clinical benefit. As pointed out in Dr. Unger's appeal, "Study 201 did not show a treatment effect on its 1° clinical endpoint, change in 6-minute walk distance at Week 24. Study 202 failed on the same endpoint at 48 weeks. The course of these Study 201/202 patients, having received eteplirsen for some 3.5 years, was not distinguishable from external control patients."[146]

[145] Eteplirsen targets a subset of patients with DMD who are amenable to exon 51 skipping.
[146] Appeal at 16.

Some may argue that it would be reasonable to proceed with accelerated approval based on eteplirsen's safety profile, even where there are significant doubts about the drug's effectiveness. That argument does not take into account the risks of treatment with indwelling catheters to maintain vascular access in young patients, who would otherwise not need one and who often receive adjunct chronic corticosteroids, or, even more importantly, the detrimental impact on their quality of life.

I would be remiss if I did not note that the sponsor has exhibited serious irresponsibility by playing a role in publishing and promoting selective data during the development of this product. Not only was there a misleading published article with respect to the results of Study 201/202[147] –which has never been retracted—but Sarepta also issued a press release relying on the misleading article and its findings. As determined by the review team, and as acknowledged by Dr. Woodcock, the article's scientific findings—with respect to the demonstrated effect of eteplirsen on both surrogate and clinical endpoints—do not withstand proper and objective analyses of the data. Sarepta's misleading communications led to unrealistic expectations and hope for DMD patients and their families. It is very disappointing that the findings did not hold up to careful review.

FDA must remain steadfast in its commitment to alleviating pain and suffering, approach the most challenging problems with absolute determination, and apply maximum flexibility to facilitate the development and availability of effective treatments. The agency's value centers on its ability to do all of the above while maintaining objectivity, even in the face of political pressure. FDA should never mislead patients by granting even accelerated approval to products that are not shown to offer the prospect of meaningful benefit to patients under the appropriate regulatory and scientific standard.

I acknowledge that there are currently no specific drugs available to treat patients with DMD and that issuance of a complete response letter would cast uncertainty on whether eteplirsen would continue to be developed, based on business and financial decisions that are external to FDA. However, approving products based on hope, on subjective clinical judgment, or on theoretical constructs that are not anchored in data leads to irreparable damage to patients. Approval at this time could deter others from pursuing the development of truly effective treatments, both for DMD and other serious, life-threatening conditions. 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.

I remain deep in my conviction that, through science and a flexible, sound regulatory approach, good therapies will emerge to provide meaningful clinical benefit to patients with DMD and other rare serious diseases.

THE SDR BOARD'S ADDITIONAL RECOMMENDATION

Although the SDR Board acknowledges that the scope of our review, as prescribed by the SDR-SMG, is limited to procedural questions, we nonetheless feel duty-bound to make one additional recommendation. As noted above, Dr. Unger seeks from the Office of the Commissioner a substantive, scientific review of Dr. Woodcock's decision to grant accelerated approval to

[147] See Mendell JR, et al. Ann Neurol 2013;74:637-47.

eteplirsen. The SDR-SMG presumes that an initiator such as Dr. Unger has received some substantive review of the scientific dispute at issue as part of a formal appeals process in the Center. Dr. Unger has never received any such formal review of his scientific arguments or the underlying evidence. To the extent he has ever received any substantive review of his scientific disagreement with Dr. Woodcock, Dr. Woodcock herself was the one who conducted that review and resolved the conflict in her own favor. Neither the SDR-SMG nor CDER's SDR-SOPs contemplate a scientific disagreement that arises between a Center Director and another manager in that same Center—partly because no one has ever anticipated the unique circumstance of this case. Especially given the SDR Board's concerns regarding the decision-making process at CDER, we think additional review within the Office of the Commissioner is appropriate.

The SDR Board encourages you to conduct a thorough substantive review of the scientific dispute in this matter or, in the alternative, to convene a panel of relevant experts to conduct such a review and provide advice to the agency and you, as Commissioner, on whether the evidence of the effect of eteplirsen on the surrogate endpoint is reasonably likely to predict clinical benefit. If you choose the latter, in light of the public and political pressure evident during the entire review process at CDER, as detailed in this recommendation, we believe that delegating this critical evaluation to a panel of experts would help ensure that the agency makes the most appropriate decision from the perspective of protecting patients and the public health, especially for DMD patients. Knowing as we do that you value cross-Center collaboration with respect to medical product development, we recommend that you include on the panel experts from other Centers devoted to the regulation of medical products. Doing so would not only help ensure diverse expertise on the panel but also provide insights on the effects that any proposed regulatory decision on eteplirsen might have on products regulated by those other Centers. We further recommend that you consider whether to include experts from other components within the Department of Health and Human Services and whether, consistent with applicable laws and the appropriate timeframe for a decision, you should also include outside experts on the panel.