United States Senate

COMMITTEE ON
HOMELAND SECURITY AND GOVERNMENTAL AFFAIRS

WASHINGTON, DC 20510–6250

September 16, 2016

Robert M. Califf, M.D.
Commissioner of Food and Drugs
U.S. Food and Drug Administration
10903 New Hampshire Avenue,
Hillandale Building, 4th Floor
Silver Spring, MD 20993

Dear Dr. Califf:

On May 25, 2016, the Food and Drug Administration (FDA) announced that it would not be able to complete its Priority Review of a New Drug Application (NDA) for a treatment of Duchenne muscular dystrophy by its goal date of May 26, 2016.[1] This goal date, which was previously extended by three months,[2] is based on guidelines established in law to encourage timely and efficient review schedules.[3] We write to express our concern about the ongoing delay to complete review of this drug and to emphasize the urgency with which all applications for drugs addressing debilitating, terminal, and rare conditions must be considered.

Congress has passed several laws giving the FDA the flexibility necessary to expedite the FDA's evaluation of new drugs for life-threatening and rare conditions and encouraging the FDA to rely on outside expertise and the patient community during the evaluation process.[4] The FDA has the authority to take into account all information presented both in the application and at the advisory committee meeting in making a decision on the safety and effectiveness of a drug. In providing the FDA with this authority, Congress recognized the need for expediency. Time is of the essence for children with rare and/or severe diseases like Duchenne and delays have costs for them that cannot be recouped.

We remain concerned that the FDA posed questions to the advisory committee during the review for a Duchenne treatment in such a way that may have confounded the evaluation of the drug's effectiveness, and in the end may have hindered consideration of the drug's merits by the

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[1] "Sarepta Therapeutics Announced FDA Will Not Complete the Review of the Eteplirsen New Drug Application By The PDUFA Date," press release, Sarepta Therapeutics, May 25, 2016.
[2] "Sarepta Therapeutics Receives Notification of PDUFA Extension for Eteplirsen," press release, Sarepta Therapeutics, February 8, 2016.
[3] 736B of the FFDCA; commitment letter found here:
http://www.fda.gov/downloads/ForIndustry/UserFees/PrescriptionDrugUserFee/UCM270412.pdf
[4] *See* Letter from Senator Ron Johnson and Senator Dan Coats to Robert Califf, M.D. (May 20, 2016) citing Food and Drug Administration Safety and Innovation Act, Pub. L. 112-144, 126 Stat. 993 (2012), Prescription Drug User Fee Act of 1992, Pub. L. no. 102-571, 106 Stat 4491 (2003), and Food and Drug Administration Modernization Act of 1997, Pub. L. no. 105-115, 111 Stat 2296 (1997).

advisory committee panel.[5] As noted recently, some feel that the committee was presented with "50-word questions littered with jargon, instead of a straightforward yes or no for approval."[6]

The Committee on Homeland Security and Governmental Affairs has been examining the FDA medical product approval process more broadly, especially as it concerns new therapies for severe and rare disease populations. This work has included a hearing of the Senate Committee on Homeland Security and Governmental Affairs on February 25, 2016, that examined policy changes intended to grant quicker access to potentially life-saving drugs where no alternative exists.[7] In addition, the Senate Committee on Health, Education, Labor, and Pensions has been focused on ways to improve medical product approval processes and expanded access policies, including passing numerous bipartisan pieces of legislation in support of that effort.

To enable the Committees to better understand FDA's current medical product approval processes and what the FDA is doing to improve the availability of necessary medical devices and treatments for patients, we ask that you please provide the following information:

1. How does the FDA ensure an efficient decision-making process between formal submission of an NDA and the agency's final review for marketing approval? How does this process differ, if at all, between review divisions? In those cases where applicable, what steps are in place to ensure an efficient process between consideration by an advisory committee or panel (in the case of a medical device) and the agency's final review for marketing approval?

2. How are questions for advisory committee and panel consideration developed? How do the FDA and/or the committees ensure they are presented with appropriate questions that do not unnecessarily hinder evaluation of the drug's effects? Can the public or committee members comment on these questions in advance of the panel?

3. Please explain the FDA's process for providing information to advisory committee members, including the following information:

    a. When do advisory committee members receive briefing materials in practice?
    b. When, on average, do members receive questions on which they can anticipate a vote?
    c. On average, how much information is contained in those briefing documents?
    d. Can advisory committee members ask questions prior to the panel regarding the briefing documents?
    e. If advisory committee members need more time prior to the panel, is there an option to allow that?

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[5] *Supra*, note 4.
[6] "Heart of Bureaucratic Darkness," *The Wall Street Journal*, editorial, Aug. 9, 2016.
[7] *Connecting Patients to New and Potential Life Saving Treatments: Hearing Before the S. Comm. on Homeland Sec. & Governmental Affairs*, 114th Cong. (2015).

4. For drugs or devices intended to address orphan disease populations, or for which finding suitable clinical trial participants is difficult, under what circumstances are studies using historical or other nonplacebo controls permitted? What policies govern the acceptance of nonplacebo studies across divisions? Are reviewers across divisions trained on those policies?

5. For the ten percent of Prescription Drug User Fee Act (PDUFA) non-compliant application reviews, how many applications remain open beyond a given year on average? How are these cases handled by the FDA to ensure they are moving toward a final decision as quickly as possible? For each review that missed the PDUFA date given, please provide a list of the time past the deadline and total time for decision.

6. What internal procedures are in place to handle disagreements about the interpretation of clinical data submitted as part of an NDA? How many days (average and median) does it take to settle internal disagreements and differences in professional interpretation of data? How does the FDA ensure that these disagreements do not lead to unnecessary delay for patients waiting on life-saving medicines?

Please produce this material as soon as possible, but by no later than 5:00 p.m. on September 30, 2016.

If you have any questions about this request, please have your staff contact Satya Thallam of Chairman Johnson's staff at (202) 224-8432 or Grace Stuntz of Chairman Alexander's staff at (202) 224-3290.

Thank you for your attention to this important matter.

Sincerely,

Ron Johnson
Chairman
Committee on Homeland Security
and Governmental Affair

Lamar Alexander
Chairman
Committee on Health,
Education, Labor
and Pensions

cc: Janet Woodcock, M.D. Director, Center for Drug Evaluation and Research

Peter Marks, M.D., Ph.D. Director, Center for Biologics Evaluation and Research

Jeffrey Shuren, M.D. Director, Center for Devices and Radiological Health