July 12, 2023

The Honorable Robert Califf, MD
Commissioner
Food and Drug Administration
10903 New Hampshire Ave.
Silver Spring, MD 20993

Dear Commissioner Califf,

As members of the Patient, Consumer, and Public Health Coalition, we appreciate your recent comments reaffirming your commitment to improving the format of Advisory Committees and look forward to working with you throughout these efforts. However, we also want to express our strong concerns when the Food and Drug Administration (FDA) Center Directors publicly undermine or privately overrule the recommendations of their own scientists' and statisticians' regarding applications for accelerated approval and full approval.

The Patient, Consumer, and Public Health Coalition is an informal coalition of nonprofit organizations representing millions of patients, consumers, researchers, and health professionals united to ensure that medical treatments are safe and effective.

At our meeting with you on March 1, you expressed your view that some nonprofit leaders and academic researchers were inaccurately and unfairly assuming that FDA Advisory Committee members were more knowledgeable than the FDA scientific reviewers who had spent months reviewing the data and other information provided by sponsors. What we have seen for several

years, particularly in recent months, is that the FDA Advisory Committee members often agree with scientific and statistical concerns and conclusions expressed in the FDA scientific memoranda provided to them to review, and it is the Center Directors or other officials that are overriding the views of FDA scientific reviewers.

Below we have summarized a few recent examples where the FDA decision conflicted with FDA scientists' and statisticians' summaries that were provided to FDA Advisory Committee members and the public.

FDA staff who presented the data at the FDA Advisory Committee meeting on May 12 regarding the accelerated approval application for Sarepta's gene therapy Elevidys made it very clear that they did not feel remotely confident that the benefits outweighed the risks for boys ages 4-7. For example, they stated that the surrogate endpoint for the drug is not "reasonably likely to predict clinical benefit" in support of accelerated approval. They also stated that although the data appeared to be more promising for boys ages 4-5, the post-hoc analysis could not be trusted. However, in his remarks, Center Director Peter Marks told the Advisory Committee that the FDA should show flexibility by granting approval. We consider this flexibility especially problematic because FDA had previously granted accelerated approval to three other Sarepta drugs, none of which have completed their confirmatory trials. In fact, the confirmatory trial for Exondys 51, which was approved in 2016, were due in November 2020 but instead was not even started until July 2020.[1]

Despite Dr. Marks' persuasive remarks at the Advisory Committee meeting, members only narrowly voted (8-6) in favor of the gene therapy, and even those who voted in favor expressed numerous concerns about the data. It has been reported that Dr. Marks overruled the recommendations of all FDA staff when he granted accelerated approval to Elevidys, consistent with what was clear for all to see at the Advisory Committee meeting.[2] Sarepta immediately announced that the treatment would cost $3.2 million per patient. Meanwhile, Sarepta is charging up to $1 million per patient per year for Exondys 51 – approximately four times the cost the company estimated in 2016. In fact, Sarepta has so far earned a total of $2.5 billion in sales from Exondys 51 and the two other Duchenne drugs granted accelerated approval.[3]

Unfortunately, the unilateral decision by CBER Director Peter Marks to overrule his own staff is troubling and harmful to the reputation of the FDA, as was the similar decision by CDER Director Janet Woodcock regarding Exondys 51 in 2016. These are just two of numerous examples where FDA Center Directors have gone against the recommendations of its own scientists and advisors to grant approval for a drug when the safety and effectiveness were not consistent with FDA requirements for approval. Two other recent examples include the controversial approval of Aduhelm (initially for all Alzheimer's patients although it was only tested on patients with mild cognitive impairment) and Relyvrio for the treatment of patients with amyotrophic lateral sclerosis (ALS). These drugs will be marketed for years without confirmation of clinical benefit.

The June 28, 2023 Advisory Committee meeting regarding a drug for Fibrodysplasia ossificans progressive (FOP) is a somewhat different example. As was the case with Elevidys, the written memorandum by FDA staff expressed strong concerns about the scientific evidence: The primary

end point was not met; the historical comparison sample was inappropriate; the data were manipulated post hoc in questionable ways; the nominal benefits were unreliable due to the wide confidence intervals; and there were increases in flare-ups – the very symptom that the drug was supposed to reduce. However, unlike the Elevidys meeting, the oral presentations by the FDA scientific and statistical staff were very obviously watered down versions of their written analyses. In fact, the main FDA presenter often seemed to be speaking on behalf of the sponsor, not the FDA. While still expressing concerns about whether the drug was safe and effective, the FDA speakers' oral presentations contradicted the written FDA documents by stating that they were confident that the treatment probably had benefit and the risks of flare-ups were probably not so serious – an odd statement given that flare-ups were the outcome measure intended to be reduced by the treatment. Those statements were dramatically inconsistent with the written document summarizing the same analyses. This would have been worrisome but more justifiable for an accelerated approval, since the drug was intended to fulfill an unmet need for a terrible disease; however, the FDA meeting was considering full approval. FDA's oral statements were so persuasive that several members of the Advisory Committee stated that the "FDA reassurances" convinced them that the benefits probably outweighed the risks, thus persuading them to vote in favor of the drug despite their strong reservations.

At an FDA Advisory Committee meeting in September 2022, FDA's scientific summary of the confirmatory trials of PI3K inhibitor duvelisib (Copiktra) concluded that the risks outweigh the benefits for patients with chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL). However, despite decreases in survival, the product retains its accelerated approval and FDA has not announced whether it intends to support those conclusions.

It is our understanding that FDA Advisory Committees are supposed to provide independent experts to review the FDA analyses, and not be unduly influenced by FDA staff or officials' urging members how they should vote. Moreover, we agreed with your remarks on March 1 that FDA scientists and statisticians are the experts with the greatest knowledge of the data and the issues involved. It undermines the integrity of the FDA, the morale of FDA staff, and the public's faith in FDA decisions when FDA officials grant an approval that contradicts its own scientists and statisticians. Equally important, overriding the scientific staff harms patients and contributes to a healthcare system that is financially unsustainable.

You have made it clear in numerous public statements that you are concerned about the format of Advisory Committee meetings, and we are as well. We urge you to speak out about the importance of FDA decisions supporting the FDA's own scientific and statistical analyses. Please consider the following recommendations as you work to improve the format of the Advisory Committees:

1. Provide training to FDA Advisory Committee members to help them understand the statistical analyses that are an essential part of all Advisory Committee meetings, and ensure they respect the importance of understanding and considering scientific evidence as part of their advisory role;
2. Require that the FDA scientific and statistical staff who write the FDA memoranda for Advisory Committee meetings have the scientific freedom to express their own views, and that those views are accurately presented in FDA oral presentations at the meeting;

3. Encourage Center Directors and other FDA officials attending Advisory Committee meetings to refrain from making comments that can be interpreted as encouraging committee members to vote a particular way; when FDA officials attend these meetings, their remarks should make it clear that FDA wants to hear their views and not to influence their votes.
4. Remind Center Directors and other FDA officials that overruling the views of their own scientific and statistical staff undermines the public trust, and should be avoided, especially when the scientific staff are in consensus.

Sincerely,

American Medical Student Association (University of Wisconsin-Madison chapter)
Breast Cancer Action
Doctors for America
Government Information Watch
Jacobs Institute of Women's Health
Medical Device Problems
MISSD
Mothers Against Medical Error
MRSA Survivors Network
National Center for Health Research
National Women's Health Network
Patient Safety Action Network
TMJ Association
USA Patient Network
Washington Advocates for Patient Safety
Woodymatters

CC:
Senator Bernie Sanders, Chair
Health, Education, Labor & Pension Committee

Senator Bill Cassidy, Ranking Member
Health, Education, Labor & Pension Committee

Representative Cathy McMorris Rodgers, Chair
Energy & Commerce Committee

Representative Frank Pallone, Ranking Member
Energy & Commerce Committee

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[1] ClinicalTrials.gov. A Study to Compare Safety and Efficacy of a High Dose of Eteplirsen in Participants With Duchenne Muscular Dystrophy (DMD) (MIS51ON). Available: https://clinicaltrials.gov/ct2/show/NCT03992430.
[2] Becker, Z. (2023). *In approving Sarepta's DMD gene therapy, FDA's Peter Marks overruled reviewer's rejection.* Fierce Pharma. Retrieved from https://www.fiercepharma.com/pharma/fda-biologics-director-peter-marks-spearheaded-sareptas-dmd-gene-therapy-approval-overruled. Accessed July. 5, 2023.

[3] Langreth, R., Rutherford, F., Milton, I., & Campbell, M. (2023). *Sarepta's gene therapy gets FDA accelerated approval: Are fast-tracked drugs safe?* Benefits Pro. https://www.benefitspro.com/2023/05/19/sareptas-gene-therapy-gets-accelerated-approval-are-fda-fast-tracked-drugs-safe/?slreturn=20230530114553. Accessed July. 5, 2023.