

**Congress of the United States**  
**House of Representatives**  
**Washington, D.C. 20515**

September 1, 2021

Janet Woodcock, M.D.  
Acting Commissioner  
U.S. Food and Drug Administration  
10903 New Hampshire Avenue  
Silver Spring, MD 20993

Dear Acting Commissioner Woodcock:

Pursuant to Rules X and XI of the U.S. House of Representatives, the Committee on Energy and Commerce and the Committee on Oversight and Reform request information from the Food and Drug Administration (FDA) regarding the review and accelerated approval of Biogen's Alzheimer's drug, Aduhelm (aducanumab).

More than six million Americans suffer from Alzheimer's disease.<sup>1</sup> Women and people of color are disproportionately impacted by Alzheimer's. Nearly two-thirds of people living with Alzheimer's in the United States are women.<sup>2</sup> Black people are twice as likely, and those who are Hispanic are one-and-one-half times as likely, as white people to develop Alzheimer's.<sup>3</sup> The number of people living with Alzheimer's in the United States is projected to increase to as many as 14 million people by 2060, affecting people of color the most.<sup>4</sup> We applaud efforts to advance brain health equity and make strides toward eradicating Alzheimer's and we share in the hope for new advancements to treat this debilitating and costly disease. However, it is critical that these treatments be safe, effective, and accessible.

We are concerned by apparent anomalies in FDA's processes surrounding its review of Aduhelm. FDA granted accelerated approval for the drug despite concerns raised by experts—including the agency's own staff and members of FDA's Peripheral and Central Nervous Systems Drugs Advisory Committee (PCNS Advisory Committee)—about the drug's clinical benefit and the use of the accelerated approval pathway for Aduhelm. We are also concerned by

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<sup>1</sup> Centers for Disease Control and Prevention, *The Truth About Aging and Dementia* ([www.cdc.gov/aging/publications/features/dementia-not-normal-aging.html](http://www.cdc.gov/aging/publications/features/dementia-not-normal-aging.html)) (accessed Aug. 27, 2021).

<sup>2</sup> UsAgainstAlzheimer's, *The Alzheimer's Disease Crisis – By the Numbers* (2021) ([www.usagainstalzhimers.org/learn/alzheimers-crisis](http://www.usagainstalzhimers.org/learn/alzheimers-crisis)) (accessed August 6, 2021).

<sup>3</sup> *Id.*

<sup>4</sup> Centers for Disease Control and Prevention, *Minorities and Women at Greater Risk for Alzheimer's Disease* ([www.cdc.gov/aging/publications/features/Alz-Greater-Risk.html](http://www.cdc.gov/aging/publications/features/Alz-Greater-Risk.html)) (accessed Aug. 27, 2021).

reports of unusual coordination between FDA and Biogen throughout the drug's approval process.

You and the leadership of FDA's Center for Drug Evaluation and Research (CDER) provided a briefing to the staffs of our committees on July 23, 2021, as well as related materials including FDA's Medical Policy and Program Review Council (MPPRC) meeting minutes. This information was helpful, but significant questions remain.

Aduhelm's approval has far-reaching implications, not only for individuals with Alzheimer's, but also for seniors, federal health care programs, and future research, development, and approval of drugs for Alzheimer's and other diseases. To help ensure that the American people continue to have the utmost confidence in FDA and the safety and efficacy of approved drugs, and to help inform future legislation, we need more information about FDA's process for reviewing and approving Aduhelm.

### **Aduhelm's Regulatory Review and Approval Process**

In September 2015, Biogen initiated two Phase 3 clinical trials designed to test the safety and efficacy of Aduhelm for individuals with early Alzheimer's disease.<sup>5</sup> The drug targets amyloid beta plaque reduction in the brain, which some research has suggested may cause Alzheimer's disease.<sup>6</sup> Following an independent data-monitoring committee report indicating the drug was unlikely to benefit people with Alzheimer's disease and that further clinical study would be futile, both trials were halted in March 2019.<sup>7</sup> In the months that followed, Biogen—in discussion with FDA—conducted a post hoc analysis of data from the cancelled clinical trials, and ultimately announced in October 2019 that the company would seek approval of Aduhelm on the basis of these findings.<sup>8</sup> Biogen submitted its Biologics License Application (BLA) for approval of Aduhelm in July 2020 and requested priority review.<sup>9</sup>

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<sup>5</sup> Biogen Inc., *Biogen Enrolls First Patient in Global Phase 3 Study of Investigational Treatment Aducanumab (BIIB037) for Early Alzheimer's Disease* (Sept. 8, 2015) (press release).

<sup>6</sup> U.S. Food and Drug Administration and Biogen Inc., *Combined FDA and Biogen Briefing Document for the November 6, 2020, Meeting of the Peripheral and Central Nervous System Drugs Advisory Committee Regarding NDA/BLA #761178, Aducanumab* (Nov. 6, 2020) ([www.fda.gov/media/143502/download](http://www.fda.gov/media/143502/download)).

<sup>7</sup> *Id.*

<sup>8</sup> *Id.*; Biogen Inc., *Biogen Plans Regulatory Filing for Aducanumab in Alzheimer's Disease Based on New Analysis of Larger Dataset from Phase 3 Studies* (Oct. 22, 2019) (press release).

<sup>9</sup> Biogen Inc., *Biogen Completes Submission of Biologics License Application to FDA for Aducanumab as a Treatment for Alzheimer's Disease* (July 8, 2020) (press release).

FDA's PCNS Advisory Committee convened on November 6, 2020, to review data pertaining to Aduhelm.<sup>10</sup> None of the 11 empaneled Advisory Committee members recommended approval.<sup>11</sup> The question of accelerated approval was not discussed at the meeting, nor were PCNS Advisory Committee members consulted on the use of amyloid beta plaque reduction as a surrogate endpoint correlated with clinical benefit during the meeting.<sup>12</sup> FDA's *Expedited Programs for Serious Conditions—Drugs and Biologics* guidance encourages drug sponsors to “communicate with the Agency early in development concerning the potential eligibility of a drug for accelerated approval, proposed surrogate endpoints or intermediate clinical endpoints, clinical trial designs, and planning and conduct of confirmatory trials.”<sup>13</sup> Notably, according to the transcript of the November 6, 2020, meeting, nearly four months after Biogen's BLA submission for approval, FDA told the PCNS Advisory Committee that it was “not using the amyloid as a surrogate for efficacy.”<sup>14</sup>

On June 7, 2021, FDA granted accelerated approval of Aduhelm—a decision that was surprising to many experts including members of the PCNS Advisory Committee.<sup>15</sup> Aduhelm was approved based on FDA's determination that clinical trial data demonstrated the drug reduced the buildup of amyloid beta plaque in the brain.<sup>16</sup> According to FDA, the reduction of amyloid beta plaque serves as a surrogate endpoint that is “reasonably likely to predict a clinical

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<sup>10</sup> U.S. Food and Drug Administration Center for Drug Evaluation and Research, *Final Summary Minutes of the Peripheral and Central Nervous System Drugs Advisory Committee Meeting* (Nov. 6, 2020) ([www.fda.gov/media/145690/download](http://www.fda.gov/media/145690/download)).

<sup>11</sup> *Id.* (All 11 members of the Advisory Committee declined to recommend approval, with ten “no” votes and one vote of “uncertain”); *Three F.D.A. Advisers Resign Over Agency's Approval of Alzheimer's Drug*, *The New York Times* (June 10, 2021); G. Caleb Alexander, M.D., et al., *Revisiting FDA Approval of Aducanumab*, *The New England Journal of Medicine* (July 28, 2021).

<sup>12</sup> See note 10.

<sup>13</sup> U.S. Food and Drug Administration, *Guidance for Industry: Expedited Programs for Serious Conditions – Drugs and Biologics* (May 2014) ([www.fda.gov/media/86377/download](http://www.fda.gov/media/86377/download)).

<sup>14</sup> U.S. Food and Drug Administration, *Transcript for the November 6, 2020, Meeting of the Peripheral and Central Nervous System Drugs Advisory Committee* (Nov. 6, 2021) ([www.fda.gov/media/145691/download](http://www.fda.gov/media/145691/download)).

<sup>15</sup> U.S. Food and Drug Administration, *FDA Grants Accelerated Approval for Alzheimer's Drug* (June 7, 2021) (press release); *The FDA's Approval of Aduhelm: Potential Implications Across a Wide Range of Health Policy Issues and Stakeholders*, *Heath Affairs Blog* (June 10, 2021); *Three F.D.A. Advisers Resign Over Agency's Approval of Alzheimer's Drug*, *The New York Times* (June 10, 2021); G. Caleb Alexander, M.D., et al., *Revisiting FDA Approval of Aducanumab*, *The New England Journal of Medicine* (July 28, 2021).

<sup>16</sup> U.S. Food and Drug Administration, *FDA Grants Accelerated Approval for Alzheimer's Drug*, (June 7, 2021) (press release).

benefit to patients” of delaying cognitive decline.<sup>17</sup> However, documents made public after the drug’s approval show that experts in FDA’s own Office of Biostatistics raised concerns about the “inconsistency” of the drug’s supporting clinical data.<sup>18</sup>

MPPRC meeting minutes raise further questions. According to these minutes, “one senior leader” suggested that the MPPRC “should consider the option of approval using AA [accelerated approval],” but “[t]here was no further discussion about the applicability of AA [accelerated approval] for aducanumab, as this option had not been presented or otherwise discussed.”<sup>19</sup> MPPRC members “concluded that another clinical trial was necessary before approving the drug,” with one member noting that approval could “result in millions of patients taking aducanumab without any indication of actually receiving any benefit, or worse, cause harm due to the relatively prevalent ARIA [amyloid-related imaging abnormalities].”<sup>20</sup>

CDER senior leadership and the Directors of the Center for Biologics Evaluation and Research and the Oncology Center of Excellence reviewed the use of the accelerated approval pathway for Aduhelm during a Center Director Briefing meeting on April 26, 2021.<sup>21</sup> According to a summary of the meeting, while five Directors supported this approach, the Director of the Office of Translational Sciences stated she “understood the arguments for and against approval” and the Director of the Office of Biostatistics “dissented on the approach, stating her belief that there is insufficient evidence to support accelerated approval or any other type of approval.”<sup>22</sup>

FDA has used surrogate endpoints to grant accelerated approval for other diseases and conditions, including for cancer and HIV.<sup>23</sup> However, experts have noted that the links between an endpoint and potential clinical benefit are well accepted in those instances, whereas the link between reduction of amyloid beta plaque and slowing cognitive decline for Alzheimer’s patients

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<sup>17</sup> *Id.*

<sup>18</sup> U.S. Food and Drug Administration, Center for Drug Evaluation Research, *Application Number: 761178Orig1s000, Statistical Review(s)* (July 7, 2020) ([www.accessdata.fda.gov/drugsatfda\\_docs/nda/2021/761178Orig1s000StatR\\_Redacted.pdf](http://www.accessdata.fda.gov/drugsatfda_docs/nda/2021/761178Orig1s000StatR_Redacted.pdf)).

<sup>19</sup> U.S. Food and Drug Administration, *Medical Policy and Program Review Council Meeting: BLA 761178, Aducanumab for the Treatment of Alzheimer’s Disease (OB, ON, OCP)* (Mar. 31, 2021 and Apr. 7, 2021) (meeting minutes).

<sup>20</sup> *Id.*

<sup>21</sup> U.S. Food and Drug Administration, *BLA #761178 Summary Memorandum* (June 7, 2021) ([www.accessdata.fda.gov/drugsatfda\\_docs/nda/2021/Aducanumab\\_BLA761178\\_Dunn\\_2021\\_06\\_07.pdf](http://www.accessdata.fda.gov/drugsatfda_docs/nda/2021/Aducanumab_BLA761178_Dunn_2021_06_07.pdf)).

<sup>22</sup> *Id.*

<sup>23</sup> U.S. Food and Drug Administration, *Development and Approval Process – Drugs* ([www.fda.gov/drugs/development-approval-process-drugs](http://www.fda.gov/drugs/development-approval-process-drugs)) (accessed Aug. 27, 2021).

“is not well-established and has even been questioned.”<sup>24</sup> Experts have also noted that prior to Aduhelm’s approval, “FDA had not indicated that it considered beta-amyloid a valid pharmacodynamic biomarker, much less an acceptable surrogate endpoint for clinical trials.”<sup>25</sup> In fact, FDA’s most recent draft guidance, published in February 2018, *Early Alzheimer’s Disease: Developing Drugs for Treatment, Guidance for Industry*, notes that for early Alzheimer’s disease trials in Stage 1 patients, “there is unfortunately at present no sufficiently reliable evidence that any observed treatment effect on such biomarker measures would be reasonably likely to predict clinical benefit.”<sup>26</sup>

### **Expert Opposition and Concerns**

Since FDA announced the approval of Aduhelm, members of the PCNS Advisory Committee, former Biogen employees, and health care providers, among others, have voiced strong opposition to Aduhelm’s approval, safety, and efficacy. Following FDA’s announcement, three PCNS Advisory Committee members resigned in protest, with one member calling it, “probably the worst drug approval decision in recent U.S. history,” and another saying he did not “wish to be part of a sham process.”<sup>27</sup> Likewise, a former Biogen senior medical director reportedly involved in designing the clinical trials for Aduhelm questioned the approval, stating, “It defeats everything I believe in scientifically and it lowers the rigor of regulatory bodies.”<sup>28</sup> In July, several major medical centers decided not to administer Aduhelm to their patients.<sup>29</sup> For example, the Cleveland Clinic’s review of Aduhelm’s safety and efficacy data by its own panel of experts led the health system to decide not to administer the drug.<sup>30</sup> More recently, the

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<sup>24</sup> *Insights on FDA’s Controversial Approval of Alzheimer’s Drug*, Johns Hopkins University Hub (June 21, 2021) ([www.hub.jhu.edu/2021/06/21/fda-aduhelm-approval/](http://www.hub.jhu.edu/2021/06/21/fda-aduhelm-approval/)).

<sup>25</sup> G. Caleb Alexander, M.D., et al., *Revisiting FDA Approval of Aducanumab*, *The New England Journal of Medicine* (July 28, 2021).

<sup>26</sup> U.S. Food and Drug Administration, *Early Alzheimer’s Disease: Developing Drugs for Treatment, Guidance for Industry* (Feb. 2018) ([www.fda.gov/media/110903/download](http://www.fda.gov/media/110903/download)). (As defined within FDA’s guidance, Stage 1 patients are those “with characteristic pathophysiologic changes of AD but no evidence of clinical impact”).

<sup>27</sup> Letter from Aaron Kesselheim, M.D., Brigham and Women’s Hospital, Harvard Medical School, to Acting Commissioner Janet Woodcock, M.D., U.S. Food and Drug Administration (June 10, 2021); *Three Experts Have Resigned from an FDA Committee Over Alzheimer’s Drug Approval*, National Public Radio (June 11, 2021); *Two Members of an FDA Advisory Committee Quit After Approval of Controversial Alzheimer’s Drug*, *The Washington Post* (June 9, 2021).

<sup>28</sup> *How an Unproven Alzheimer’s Drug Got Approved*, *The New York Times* (July 19, 2021).

<sup>29</sup> *Cleveland Clinic and Mount Sinai Won’t Administer Aduhelm to Patients*, *The New York Times* (July 14, 2021).

<sup>30</sup> *Id.*

Department of Veterans Affairs (VA) confirmed that Aduhelm will not be added to the VA National Formulary “due to the risk of significant adverse drug events and to the lack of evidence of a positive impact on cognition.”<sup>31</sup>

FDA’s labeling decision for Aduhelm also “surprised and concerned” experts, even those who supported the drug’s approval.<sup>32</sup> Although clinical trials were only conducted on early-stage Alzheimer’s patients and those with mild cognitive impairment, accounting for approximately 1.5 million patients in the United States, the label for Aduhelm allows use of the drug “for the treatment of Alzheimer’s disease”—a broader patient population that may include more than six million people.<sup>33</sup> On July 8, 2021, FDA approved Biogen’s updated prescribing information for Aduhelm, which now notes that treatment “should be initiated in patients with mild cognitive impairment or mild dementia stage of disease, the population in which treatment was initiated in clinical trials.”<sup>34</sup> While the amended label specifies that there is no safety or effectiveness data for treating other stages of the disease, it does not change the broad indication “for the treatment of Alzheimer’s disease.”<sup>35</sup>

### **Reports of Potentially Improper Interactions Between FDA and Biogen**

Information that has come to light since Aduhelm’s approval also indicates that interactions between FDA and Biogen throughout Aduhelm’s approval process may have been contrary to FDA’s own guidance for staff engagement with sponsors during drug development. In May 2019, following Biogen’s decision to halt clinical trials for Aduhelm, a Biogen official arranged for an “off-the-books” meeting to share data and explore potential avenues for approval with FDA’s Director of the Office of Neuroscience.<sup>36</sup> Subsequently, FDA and Biogen reportedly

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<sup>31</sup> *Scoop: VA decides against adding Biogen's Aduhelm to its formulary as PBM shuns controversial Alzheimer's drug*, EndPoints News (Aug. 11, 2021).

<sup>32</sup> *Many Alzheimer’s Experts Say Use of Aduhelm Should Be Sharply Limited*, The New York Times (June 21, 2021).

<sup>33</sup> U.S. Food and Drug Administration, *Aduhelm Label* ([www.accessdata.fda.gov/drugsatfda\\_docs/label/2021/761178s000lbl.pdf](http://www.accessdata.fda.gov/drugsatfda_docs/label/2021/761178s000lbl.pdf)) (accessed Aug. 27, 2021); *F.D.A. Approves Alzheimer’s Drug Despite Fierce Debate Over Whether It Works*, The New York Times (June 7, 2021); *New Drug Could Cost the Government as Much as It Spends on NASA*, The New York Times (June 22, 2021).

<sup>34</sup> Biogen Inc., *FDA Approves Updated ADUHELM™ Prescribing Information to Emphasize Population Studied in Clinical Trials* (July 8, 2021) (press release).

<sup>35</sup> *Id.*

<sup>36</sup> *Inside ‘Project Onyx’: How Biogen Used an FDA Back Channel to Win Approval of Its Polarizing Alzheimer’s Drug*, STAT News (June 29, 2021); *How an Unproven Alzheimer’s Drug Got Approved*, The New York Times (July 19, 2021) (During FDA’s July 23, 2021, briefing to Committee staffs, agency officials appeared to confirm the existence of this meeting, noting they were unaware of the substance of the discussion).

convened a “working group” of Biogen employees and FDA officials, which “met or communicated almost daily” throughout the summer of 2019.<sup>37</sup>

Communication and the exchange of data between FDA and drug sponsors is a necessary component of a drug’s approval process. FDA officials asserted during the July 23, 2021, staff briefing that it may also be commonplace for some of this communication to occur as informal discussion between FDA and the drug sponsor.<sup>38</sup> However, FDA officials also acknowledged in the staff briefing that not all communication with Biogen officials was memorialized, counter to FDA’s best practices.<sup>39</sup> In the spring of 2021, FDA initiated an internal assessment led by CDER staff, of the agency’s collaboration with Biogen.<sup>40</sup>

We commend all actions to assess and address any potential improprieties in order to strengthen public trust in FDA and its processes. In particular, we applaud your July 9, 2021, request that the Department of Health and Human Services (HHS) Office of the Inspector General (OIG) investigate the interactions between FDA and Biogen.<sup>41</sup> We are also pleased that on August 4, 2021, HHS OIG announced it would review FDA’s interactions with outside entities as well as how “FDA implements the accelerated approval pathway” and “aspects of the process, such as deciding on this pathway and scientific disputes.”<sup>42</sup> OIG indicated the work

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<sup>37</sup> *Inside ‘Project Onyx’: How Biogen Used an FDA Back Channel to Win Approval of Its Polarizing Alzheimer’s Drug*, STAT News (June 29, 2021).

<sup>38</sup> Briefing by U.S. Food and Drug Administration to House Committee on Energy and Commerce Staff and House Committee on Oversight and Reform Staff (July 23, 2021).

<sup>39</sup> U.S. Food and Drug Administration, *Best Practices for Communication Between Drug Sponsors and FDA During Drug Development: Guidance for Industry and Review Staff* (Dec. 2017) ([www.fda.gov/media/94850/download](http://www.fda.gov/media/94850/download)); 21 C.F.R. § 312.47 (2010).

<sup>40</sup> *How an Unproven Alzheimer’s Drug Got Approved*, New York Times (July 19, 2021); Briefing by U.S. Food and Drug Administration, to House Committee on Energy & Commerce Staff and House Committee on Oversight and Reform Staff (July 23, 2021) (The internal assessment followed letters from Public Citizen raising concerns about “Aduhelm’s development, presentation to the PCNS Advisory Committee, and approval process.” See Letter from Michael A. Carome, M.D., Director, Public Citizen’s Health Research Group, to Commissioner Stephen M. Hahn, M.D., U.S. Food and Drug Administration, and Acting Director Patrizia Cavazzoni, M.D., Center for Drug Evaluation and Research, U.S. Food and Drug Administration (Dec. 9, 2020); Letter from Michael A. Carome, M.D., Director, Public Citizen’s Health Research Group, to Acting Commissioner Janet Woodcock, M.D., U.S. Food and Drug Administration (Jan. 28, 2021)).

<sup>41</sup> Letter from Acting Commissioner Janet Woodcock, M.D., U.S. Food and Drug Administration, to Acting Inspector General Christi A. Grimm, U.S. Department of Health and Human Services (July 9, 2021).

<sup>42</sup> *HHS Watchdog to Probe FDA’s Use of Accelerated Approval Process for Drugs*, Politico (Aug. 4, 2021); U.S. Department of Health and Human Services, Office of Inspector General, Review of the FDA’s Accelerated Approval Pathway ([oig.hhs.gov/reports-and-](http://oig.hhs.gov/reports-and-)

may result in multiple reports with an expected issue date of 2023.<sup>43</sup> While we look forward to OIG's findings, Congress and the American people need answers and clarity on Aduhelm's approval as soon as possible.

To assist the committees with this investigation, we request that you provide the following information and documents by September 16, 2021.

1. There does not appear to be consensus among experts that amyloid beta plaque is an acceptable surrogate endpoint for demonstrating a clinical benefit for Alzheimer's patients. What body of evidence did FDA rely on to determine the use of amyloid beta plaque as a surrogate endpoint is "reasonably likely to predict clinical benefit" for Alzheimer's disease?
  - a. Please specify the clinical trial data from Biogen's Aduhelm clinical studies, or other evidence, FDA relied upon in determining the drug product met the qualifying criteria for accelerated approval. How does FDA reconcile its determination that the drug met the criteria for accelerated approval with that of the PCNS Advisory Committee, some of FDA's own experts, and some of the nation's largest medical centers and insurers who have determined there is insufficient data on the safety and efficacy of Aduhelm to warrant approval?
  - b. Did FDA consider posing the question of accelerated approval to the PCNS Advisory Committee either prior to or after the November 2020 meeting? If so, who participated in any discussions, who ultimately made the decision to proceed without bringing that question back to the Advisory Committee, and why?
  - c. Does FDA plan to update its February 2018 *Early Alzheimer's Disease: Developing Drugs for Treatments Draft Guidance for Industry* as a result of the decision to grant accelerated approval for Aduhelm? If so, what is the planned timeline for such revision? If not, please explain why.
2. What process was used to determine which questions would be submitted to the PCNS Advisory Committee for discussion at the November 6, 2020, meeting? Is this the process used by FDA for all Advisory Committee meetings? If the process for Aduhelm differed from other Advisory Committee meetings, how did the process differ and why?
3. What, if any, additional steps did FDA consider taking to further evaluate whether Aduhelm should be approved following the unanimous lack of affirmative

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publications/workplan/summary/wp-summary-0000608.asp) (accessed Aug. 30, 2021).

<sup>43</sup> U.S. Department of Health and Human Services, Office of Inspector General, *Review of the FDA's Accelerated Approval Pathway* (oig.hhs.gov/reports-and-publications/workplan/summary/wp-summary-0000608.asp) (accessed Aug. 30, 2021).



recommendation for approval of the drug from the PCNS Advisory Committee?

- a. Who requested input from FDA's MPPRC on whether to approve aducanumab based on the evidence of effectiveness provided by Biogen's Phase 1 trial and two cancelled Phase 3 studies?
  - b. Why was the option of accelerated approval not brought back to the MPPRC for discussions and who made this decision?
  - c. How were participants selected for the April 26, 2021, Center Director Briefing meeting and who determined the topic for discussion? Please provide the April 26, 2021, meeting minutes and any related materials.
  - d. Please provide all other examples of when FDA has proceeded with a Center Director Briefing vote on approval for a drug using an approval pathway option not considered by either the Advisory Committee or the MPPRC.
4. In addition to responses to the following questions, please provide a list of each respective approval granted and the corresponding Advisory Committee vote as applicable.
- a. How many times has FDA issued a standard approval or accelerated approval for a drug contrary to the majority vote of its respective Advisory Committee?
  - b. How many times has FDA issued an approval without a single vote recommending approval from its respective Advisory Committee?
  - c. How many times has FDA issued an accelerated approval instead of a standard approval following Advisory Committee consideration only of standard approval?
5. What process or related policies, if any, are in place for making an approval determination when there is FDA staff disagreement with the Advisory Committee and/or when there is internal disagreement among the relevant FDA expert reviewers?
- a. Did Aduhelm's approval process deviate from this process or related policies? If so, please describe how and who made each respective decision.
  - b. Who ultimately makes the decision whether to approve the drug following a disagreement internally or with the Advisory Committee?
6. When did FDA first discuss the potential use of the accelerated approval pathway for Aduhelm internally, and who was a part of any such discussions?
- a. When did FDA first discuss the accelerated approval pathway with Biogen, and who was a part of any such discussions?

- b. Please identify any officials involved in the decision to approve Aduhelm not otherwise identified in public documents or materials otherwise provided to the committees.
7. When did FDA initiate its internal assessment of interactions between FDA personnel and Biogen related to the approval of Aduhelm?
  - a. What is the status of this internal assessment and any other internal reviews or assessments? Please identify who led this internal assessment and any individuals who have been briefed on the status of the assessment or who have been provided relevant or related findings.
  - b. Is the agency continuing to discuss or conduct any additional internal reviews or other assessments related to Aduhelm's approval?
  - c. What, if any actions or changes have been implemented as a result of the findings?
  - d. Please provide any documents, including communications, related to any internal reviews or assessments concerning the approval of Aduhelm, including any draft or final findings, recommendations, or reports.
8. Please provide a list of formal and informal conversations and meetings between FDA and any representative of Biogen, and all documents, including communications, related to those conversations since January 2018.
  - a. Please specify which conversations or meetings were not memorialized, the participants of those conversations or meetings, a summary of the purpose of each meeting, and why they were not memorialized.
9. When did the first conversation or communication occur regarding a post hoc analysis of data from the cancelled clinical trials among any FDA staff and any representative of Biogen?
  - a. If, as reported, a "working group" was developed, how was it structured, who participated in the group, and how often did it meet and/or communicate?
  - b. How common is it for FDA to consult, advise, or conduct such a statistical post hoc analyses of clinical trials, including those that have been halted prior to conclusion? Please provide a list of when this has occurred before, if ever.
10. Please describe any communications between FDA and Biogen in preparation for the November 6, 2020, PCNS Advisory Committee meeting.

- a. How many times has FDA jointly authored a primary briefing document for an Advisory Committee meeting with a drug sponsor?
  - b. Why did FDA decide to jointly author such a document in this case?
  - c. Please describe the process for drafting FDA's sections of this joint briefing document and whether FDA allowed Biogen the opportunity to review and edit the FDA sections of the document.
  - d. Is it common practice for FDA to allow drug sponsors to review and provide feedback to FDA's internal expert review materials?
11. Please provide a list of any third-party entities FDA was in communication with regarding the approval of Aduhelm, including the extent and purpose of such communication.
12. What internal discussions did FDA have regarding Aduhelm's proposed indication?
- a. Why did FDA approve Aduhelm for a broader treatment indication than what was studied in the clinical trials? Did FDA consider approving an indication to reflect the clinical trial population? If this was considered, why did the agency not take this action? If not considered, please explain why.
  - b. What led FDA to revise Aduhelm's prescribing information in the month following Aduhelm's approval?
  - c. What was the internal process for this label update, who participated in these discussions, and who ultimately made the determination?
  - d. Did FDA communicate with Biogen about the label for Aduhelm, including the initial approval label and the July 8, 2021, update? Please specify when these conversations occurred, who participated in these conversations, and provide any documents, including communications, related to the label for Aduhelm.
13. Did any FDA staff participate in any projects or presentations with representatives of Biogen while the company had applications pending before the FDA? If so, please list all such collaborative efforts, the individuals involved, the nature of the collaboration, and who approved the collaboration.
- a. What is the process for obtaining approval to collaborate on a project with a sponsor who has an application pending before the agency?
  - b. Was that process followed in each instance detailed in the response to question 13?

14. When did FDA first discuss postmarketing Phase 4 trial(s) for Aduhelm with Biogen? How and why was a nine-year timeline agreed to for the postmarketing trial(s), and does this meet FDA's own guidance, set forth in *Expedited Programs for Serious Conditions—Drugs and Biologics*, that such trials be completed with due diligence, meaning the trial to verify the clinical benefit be “conducted promptly”?<sup>44</sup>
- a. What agreement did FDA reach with Biogen about the design and conduct of the trial before Aduhelm's approval? If no such agreement was reached, who made that decision and why not?
  - b. What, if any, benchmarks will FDA require of Biogen toward the completion of the postmarketing Phase 4 trial(s) prior to 2030?
  - c. What tools does FDA have to enforce these benchmarks and ensure completion of the postmarketing Phase 4 trial(s)?
  - d. What, if any, support will FDA provide to ensure the expediency and diversity of the postmarketing Phase 4 trial(s) participant enrollment?
15. What steps will FDA take to communicate progress of the postmarketing Phase 4 trial(s) to Congress, providers, Alzheimer's patients and families, and the broader public?

An attachment to this letter provides additional instructions for responding to the committees' request. If you have any questions regarding this request, please contact Energy and Commerce Committee staff at (202) 225-2927 or Oversight and Reform Committee staff at (202) 225-5051. Thank you for your prompt attention to this matter.

Sincerely,



Frank Pallone, Jr.  
Chairman  
Committee on Energy and Commerce



Carolyn B. Maloney  
Chairwoman  
Committee on Oversight and Reform

Enclosure

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<sup>44</sup> See note 13.

Janet Woodcock, M.D.

September 1, 2021

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cc: The Honorable Cathy McMorris Rogers  
Ranking Member  
Committee on Energy and Commerce

The Honorable James Comer  
Ranking Member  
Committee on Oversight and Reform