VIA ELECTRONIC SUBMISSION

September 25, 2023

Patrizia A. Cavazzoni, M.D., Director
Center for Drug Evaluation and Research
Food and Drug Administration
10903 New Hampshire Ave
Silver Spring, MD 20993

[Docket No. FDA-2023-N-3167]

Dear Director Cavazzoni,

Arnold Ventures welcomes the opportunity to provide comments to the U.S. Food and Drug Administration's (FDA) Center for Drug Evaluation and Research on the following notice issued August 25, 2023:

- *Notice of Opportunity for Public Comment on Proposal to Withdraw Approval of New Drug Application for PEPAXTO, Equivalent to 20 Milligrams Base per Vial*

Arnold Ventures (AV) is a philanthropy dedicated to investing in evidence-based policy solutions that maximize opportunity and minimize injustice. Our work within the health care sector is driven by the recognition that the system costs too much and fails to adequately care for the people it serves. Our work spans a range of issues including commercial-sector prices, provider payment incentives, prescription drug prices, clinical trials, Medicare sustainability, and complex care.

AV supports the agency's proposal[i] to withdraw the accelerated approval of PEPAXTO given the totality of evidence, lack of clinical benefit for patients, and increased risk of adverse events. We view PEPAXTO's proposed withdrawal as an opportunity to request that the Secretary issue draft guidance required by the Consolidated Appropriations Act of 2023 ("the Act") that (1) describes the expedited withdrawal procedures that will be used moving forward, and (2) addresses ways to make the withdrawal process timelier than the one used for PEPAXTO.

Expedited withdrawal is warranted when a required post-approval confirmatory trial fails to verify clinical benefit. When the available evidence demonstrates a drug is not shown to be safe or effective under its conditions of use, FDA must develop and use procedures to withdraw approval of that drug expeditiously. This ensures that (1) patients are not using drugs that are ineffective and/or potentially unsafe, and (2) health care dollars are directed toward interventions that have more meaningful evidence documenting safety and efficacy.

AV is concerned with the amount of time it took FDA to formally withdraw PEPAXTO under the Accelerated Approval Program. The Act added four necessary steps for expedited withdrawal procedures, including notice, explanation, opportunity for appeal, and public comment period. However, the precipitating events that led FDA to initiate withdrawal are also worth examining. To this end, we provided a table at the end of this letter that outlines the timeline from publication of PEPAXTO's clinical trial results to withdrawal notice by FDA, including procedures cited in the Act. We observed over two years passed from the time FDA alerted the public of an increased

risk of death associated with PEPAXTO to the FDA withdrawal request. There were notable gaps of inaction by FDA. We ask that FDA consider ways to expedite this timeline when developing guidance in response to Congress and under the Act.

We encourage FDA and other policymakers to consider the financial and physical consequences of patient exposure to accelerated approval drugs that fail their confirmatory trials in future reforms to the accelerated approval pathway.[ii] We urge FDA to consider solutions that generate evidence on drugs with accelerated approval in a timely manner to protect patient safety.[iii] This includes:

- Requiring any expedited withdrawal meetings with manufacturers to be held publicly because the drug affects a broad and diverse collection of stakeholders, and
- Initiating future expedited withdrawals shortly after either alert to increased risk of death from a drug indication or target date of study completion for confirmatory studies of products with accelerated approval.

Arnold Ventures is prepared to assist with any additional information needed to address these comments upon review. Comments were prepared by Katherine Szarama, Ph.D., Director of Health Care and Kirk Williamson, MPH, Manager of Health Care with assistance from Andrea Noda, MPP, Vice President of Health Care and Mark E. Miller, Ph.D., Executive Vice President of Health Care at Arnold Ventures.

Please contact Andrea Noda at anoda@arnoldventures.org or Mark E. Miller, Ph.D. at mmiller@arnoldventures.org with any questions. We thank FDA and its staff for its important work protecting public health by ensuring the safety and efficacy of human drugs and biological products.

Sincerely,

Andrea Noda

Timeline from publication of PEPAXTO's clinical trial results to withdrawal notice by FDA

June 2017	PEPAXTO Phase III Clinical Trial listed publicly[iv]
February 2021	PEPAXTO Accelerated Approval by FDA[v]
March 2021	Phase II Clinical Trial results published[vi]
May 2021	Manufacturer's Investor Presentation of Phase III Clinical Trial[vii]
July 2021	FDA Alert: increased risk of death associated with PEPAXTO[viii]
October 2021	Manufacturer's Voluntary Withdrawal of PEPAXTO[ix]
January 2022	Manufacturer rescinds voluntary withdrawal and publishes results of Phase III Clinical Trial[x]
September 2022	FDA Advisory Committee voted (14-2) that the benefit-risk profile of PEPAXTO is not favorable for the currently indicated patient population.[xi]
December 2022	FDA requests voluntary withdrawal of PEPAXTO[xii]
July 2023	FDA notice explaining expedited withdrawal of PEPAXTO[xiii]
August 2023	Manufacturer appeals expedited withdrawal of PEPAXTO[xiv]

[i] https://downloads.regulations.gov/FDA-2023-N-3167-0002/attachment_1.pdf
[ii] https://jamanetwork.com/journals/jamaoncology/fullarticle/2801800
[iii] https://craftmediabucket.s3.amazonaws.com/uploads/AV-AcceleratedApprovalIssueBrief-v4.pdf
[iv] https://clinicaltrials.gov/study/NCT03151811?a=48
[v] https://www.fda.gov/drugs/resources-information-approved-drugs/fda-grants-accelerated-approval-melphalan-flufenamide-relapsed-or-refractory-multiple-myeloma
[vi] https://pubmed.ncbi.nlm.nih.gov/33296242/

[vii] https://www.oncopeptides.com/en/investors/investor-presentations/webcast-presentation-of-ocean-topline-results-may-25-2021
[viii] https://www.fda.gov/drugs/drug-safety-and-availability/fda-alerts-patients-and-health-care-professionals-about-clinical-trial-results-showing-increased
[ix] https://www.oncopeptides.com/en/investors/investor-presentations/webcast-oncopeptides-withdraw-pepaxto--in-us-scale-down-organization-and-focus-on-rd
[x] https://pubmed.ncbi.nlm.nih.gov/35032434/

[xi] https://www.fda.gov/advisory-committees/advisory-committee-calendar/september-22-23-2022-meeting-oncologic-drugs-advisory-committee-announcement-09222022
[xii] https://www.oncopeptides.com/en/media/press-releases/oncopeptides-provides-update-on-pepaxto-us-marketing-authorization
[xiii] https://www.regulations.gov/document/FDA-2023-N-3167-0002
[xiv] https://www.regulations.gov/document/FDA-2023-N-3167-0005