To Whom It May Concern,

On behalf of Doctors for America's Food and Drug Administration (FDA) Task Force, thank you for your work to reauthorize the FDA's user fee programs. Doctors for America (DFA) is an independent, non-partisan organization of over 27,000 physicians and medical trainees from across the country dedicated to advancing policies that prioritize our patients ahead of our profession and politics. DFA does not take any funding from the pharmaceutical and medical device industry. The FDA Task Force within DFA and its clinician members have a sole focus on strengthening and supporting the FDA in its work of protecting our patients and ensuring timely access to truly safe and effective health technologies.

We write today to urge you to make the following changes to the *Food and Drug Administration Safety and Landmark Advancements (FDASLA) Act* before the bill is signed into law. Each change is crucial to uphold the FDA's mission of ensuring that the medical products that we prescribe to our patients are safe and clinically effective.

1. **Include automatic expiration of drugs approved under accelerated approval that fail to show benefit in post-approval studies after five years.**

Currently, the FDA relies on manufacturers to voluntarily withdraw their drugs from the market, which may occur long after patients have suffered medical and financial harms. A recent study showed that 10% of drugs granted accelerated approval had no proven clinical benefit and remained available for patients for more than five years. In order to protect patients from unnecessary harm, this bill must include automatic withdrawal of drugs for which clinical benefit has not been proven five years following accelerated approval.

2. **Mandate post-approval studies for all drugs approved under accelerated approval.**

Accelerated approval drugs are approved by the FDA based on a surrogate endpoint (e.g. changes of a lab test value or in imaging) thought to be predictive of meaningful, clinical benefit for patients (e.g. reduction in deaths or hospitalizations). In our recently published study, we also found that for drugs approved through the accelerated pathway between 2015 and 2017, Medicare and Medicaid have spent over $40 billion on drugs whose postapproval confirmatory trials used surrogate endpoints rather than clinical endpoints demonstrating meaningful effects of drugs on how patients feel, function, or survive. In exchange for earlier access for patients to potentially promising treatments, manufacturers must be required to complete confirmatory post-approval studies that truly confirm the drug's predicted clinical benefit.

3. **Require FDA to convene advisory committee meetings for all accelerated approval drugs.**

Recent research has found that FDA has less often convened their own advisory committees of independent experts over time. FDA convened these committees of independent experts for 55% of drugs approved annually

in 2010 to 6% in 2021. Particularly for accelerated approval drugs where approval is based on less evidence, FDA must convene these experts to offer their recommendations for these approvals. These committees should also be consulted in the design of postapproval studies to ensure that these required confirmatory trials are structured to ascertain true clinical benefit for patients.

4. **Clarify that Real-World Evidence should only augment post-approval studies, not fully support.**

Prior research has shown that none of the required confirmatory trials for drugs granted accelerated approval between 2009 and 2018 could be replicated using existing real-world evidence such as electronic health record or medical claims data. Real world evidence can be used to supplement clinical trial data, but is insufficient for demonstrating clinical benefit of accelerated approval drugs. Patients deserve to have access to speedy therapy but not at the risk of ineffective, and sometimes dangerous outcomes.

5. **Any FDA user fee legislation must include enforceable measures to ensure clinical trial diversity and to hold sponsors accountable should they not ensure adequate representation in their studies.**

Currently, FDASLA does not include any provisions to ensure adequate representation across age, gender, and race/ethnicity of studies supporting FDA approval of new medical products. Such policies are critical for ensuring that sponsors are testing their treatments in trial participants that reflect patients who ultimately will be prescribed the drug or device. While FDA has made efforts to encourage sponsors to increase diversity in their clinical trials, these have not been sufficient. Various studies have shown that pivotal trials over time have failed to enroll certain subpopulations of patients. FDA has recently issued guidance to recommend -- but not require – sponsors submit race and ethnicity diversity plans, but without enforcement mechanisms, it is unclear if sponsors will adhere to this recommendation. The National Academies of Science, Engineering, and Medicine also recently released a report on *Improving Representation in Clinical Trials and Research: Building Research Equity for Women and Underrepresented Groups*, which includes several actionable recommendations that should be included as part of the user fee legislation.

In Appendix A, you will find the proposed amendments specifically related to the accelerated approval pathway as well as why these are important based on medical literature and clinical practice. Also attached are line by line amendments to FDASLA including provisions to ensure clinical trial diversity.

Patients deserve the assurance that the drugs they are prescribed have been proven effective based on the highest evidentiary standards. Patients and providers need speedy access to therapies that are both safe and effective. Please reach out to me with any questions.

Sincerely,

Reshma Ramachandran, MD MPP
Chair, Doctors for America FDA Task Force
Co-Director, Yale Collaboration for Research Integrity and Transparency (CRIT)

Appendix A: Amendment Language to FDASLA

Section 506. MODERNIZING ACCELERATED APPROVAL

1) Postapproval studies for all accelerated approval drugs should be required to confirm their clinical benefit and FDA should convene advisory committees

Draft Bill Language: (a) IN GENERAL. – Section 506(c) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 356(c)) is amended—

(1) in paragraph (2)—

(A) by redesignating subparagraphs (A) and (B) as clauses (i) and (ii), respectively, and adjusting the margins accordingly;

(B) by striking "Approval of a product" and inserting the following:

"(A) In General.—Approval of a product";

(C) in clause (i) of such subparagraph (A), as so redesignated, by striking ''appropriate postapproval studies'' and inserting ''an appropriate postapproval study or studies…; and

(D) by adding at the end the following:

''(B) STUDIES NOT REQUIRED. —If the Secretary does not require that the sponsor of a product approved under accelerated approval conduct a postapproval study under this paragraph, the Secretary shall publish on the website of the Food and Drug Administration the rationale for why such study is not appropriate or necessary.

Amendment: (a) IN GENERAL. – Section 506(c) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 356(c)) is amended—

(1) in paragraph (2)—

(A) by redesignating subparagraphs (A) and (B) as clauses (i) and (ii), respectively, and adjusting the margins accordingly;

(B) by striking "Approval of a product" and inserting the following:

"(A) In General.—Approval of a product shall be subject to the following requirements";

(C) in clause (i) of such subparagraph (A), as so redesignated, by striking ''appropriate postapproval studies'' and inserting ''an appropriate postapproval study or studies…; and

(D) by adding at the end the following:

~~''(B) STUDIES NOT REQUIRED. —If the Secretary does not require that the sponsor of a product approved under accelerated approval conduct a postapproval study under this paragraph, the Secretary shall publish on the website of the Food and Drug Administration the rationale for why such study is not appropriate or necessary.~~

Justification: Accelerated approval drugs are approved by the FDA based on a surrogate endpoint (e.g. changes of a lab test value or in imaging) thought to be predictive of meaningful, clinical benefit for patients (e.g. reduction in deaths or hospitalizations). In exchange for earlier access for patients to potentially promising treatments, manufacturers are expected to complete confirmatory postapproval studies that confirm the drug's predicted clinical benefit. These studies are critical in providing certainty to patients and clinicians that these unproven treatments truly have a meaningful clinical benefit and thus, the FDA should require these studies.

NOTE: Short of this amendment that would allow FDA to require postapproval studies for all accelerated approval drugs, the proposed section within the draft legislation entitled "STUDIES NOT REQUIRED" could be considered where FDA would have to make transparent their rationale for not requiring such studies.

2) FDA should be required to convene advisory committees for all accelerated approval drugs.

Draft Bill Language: (a) IN GENERAL. – Section 506(c) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 356(c)) is amended—

(1) in paragraph (2)—

(A) by redesignating subparagraphs (A) and (B) as clauses (i) and (ii), respectively, and adjusting the margins accordingly;

(B) by striking "Approval of a product" and inserting the following:

"(A) In General.—Approval of a product";

(C) in clause (i) of such subparagraph (A), as so redesignated, by striking ''appropriate postapproval studies'' and inserting ''an appropriate postapproval study or studies…; and

(D) by adding at the end the following:

''(B) STUDIES NOT REQUIRED. —If the Secretary does not require that the sponsor of a product approved under accelerated approval conduct a postapproval study under this paragraph, the Secretary shall publish on the website of the Food and Drug Administration the rationale for why such study is not appropriate or necessary.

Amendment: (a) IN GENERAL. – Section 506(c) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 356(c)) is amended—

(1) in paragraph (2)—

(A) by redesignating subparagraphs (A) and (B) as clauses (i) and (ii), respectively, and adjusting the margins accordingly;

(B) by striking "Approval of a product" and inserting the following:

"(A) In General.—Approval of a product shall be subject to the following requirements";

(C) in clause (i) of such subparagraph (A), as so redesignated, by striking ''appropriate postapproval studies'' and inserting ''an appropriate postapproval study or studies…; and

(D) by adding at the end the following:

~~''(B) STUDIES NOT REQUIRED.—If the Secretary does not require that the sponsor of a product approved under accelerated approval conduct a postapproval study under this paragraph, the Secretary shall publish on the website of the Food and Drug Administration the rationale for why such study is not appropriate or necessary.~~

''(iii) That the Secretary convene and consult an advisory committee on the evidentiary standards for accelerated approval as well as the design of postapproval studies to verify and describe the predicted effect on irreversible morbidity or mortality or other clinical benefit.

Justification: Recent research has found that FDA has less often convened their own advisory committees of independent experts over time. Between 2010 and 2021, FDA went from convening these committees for 55% to 6% of approved drugs annually. Particularly for accelerated approval drugs where approval is based on less evidence, FDA should convene these experts to offer their recommendations for these approvals and also discuss the design of postapproval studies.

3) Real-world evidence should be allowed to complement, not supplant clinical trials to fulfill postapproval study requirements.

Draft Bill Language: "(A) In General.—Approval of a product";

(C) in clause (i) of such subparagraph (A), as so redesignated, by striking ''appropriate postapproval studies'' and inserting ''an appropriate postapproval study or studies (which may be augmented or supported by real world evidence)"; and

Amendment: "(A) In General.—Approval of a product";

(C) in clause (i) of such subparagraph (A), as so redesignated, by striking ''appropriate postapproval studies'' and inserting ''an appropriate postapproval study or studies (which may be augmented ~~or supported~~ by real world evidence)"; and

Justification: Prior research has shown that none of the required confirmatory trials for drugs granted accelerated approval between 209 and 2018 could be replicated using existing real-world evidence such as electronic health record or medical claims data. Thus, this demonstrates that existing real-world evidence is insufficient for demonstrating clinical benefit of accelerated approval drugs, but could be used to supplement clinical trial data.

4) Automatic expiration of unproven accelerated approval drugs should be reinstated

Amendment: (following (B) EXPEDITED PROCEDURES) (C) AUTOMATIC EXPIRATION.—The approval of a product approved under accelerated approval after the date of enactment of the Accelerated Approval Integrity Act of 2022 shall automatically expire 1 year after any target date of study completion included in an agreement described in clause(ii) of paragraph(2)(A), and in no case later than 5 years after the date on which the product is approved, unless—

''(i) a study required to verify and describe the predicted effect on irreversible morbidity or mortality or other clinical benefit of the product has verified that predicted effect; or

''(ii) the Secretary has determined that adequate progress has been made on completion of postapproval studies required under paragraph (2)(A).

Justification: Accelerated approval drugs remain on the market for years despite manufacturers failing to initiate or demonstrate clinical benefit. An investigation from the *The BMJ* found that 10% of drugs granted accelerated approval had no proven clinical benefit and remained available for patients for more than 5 years. Due to the current, lengthy process for FDA to withdraw accelerated approval drugs with no proven clinical benefit, the agency instead relies on manufacturers to voluntarily withdraw their drugs from the market instead, which may occur long after patients have suffered medical and financial harms. Research has shown that the median duration for completing postapproval studies is 17 months, so 5 years following accelerated approval would be a generous allowance.

5) Unnecessary barriers to withdrawing unproven accelerated approval drugs from the market should be removed.

Draft Bill Language: (B) EXPEDITED PROCEDURES DESCRIBED.— Expedited procedures described in this subparagraph shall consist of, prior to the withdrawal of accelerated approval—

(i) providing the sponsor with—

(I) due notice;

(II) an explanation of the proposed withdrawal;

(III) an opportunity for a meeting with the Commissioner of Food and Drugs or the Commissioner's designee; and

(IV) an opportunity for written appeal to—

(aa) the Commissioner of Food and Drugs; or

(bb) a designee of the commissioner who has not participated in the proposed withdrawal of approval (other than a meeting pursuant to subclause (III)) and is not a subordinate of an individual (other than the Commissioner) who participated in such proposed withdrawal;

(i) providing an opportunity for public comment on the notice proposing to withdraw approval;
(ii) the publication of a summary of the public comments received, and the Secretary's response to such comments, on the website of the Food and Drug Administration; and
(iii) convening and consulting an advisory committee on issues related to the proposed withdrawal, if requested by the sponsor and if no such advisory committee has previously advised the Secretary on such issues with respect to the withdrawal of the product prior to the sponsor's request.

Amendment: (B) EXPEDITED PROCEDURES DESCRIBED.— Expedited procedures described in this subparagraph shall consist of, prior to the withdrawal of accelerated approval—

(i) providing the sponsor with—

(I) due notice;

(II) an explanation of the proposed withdrawal;

~~(III) an opportunity for a meeting with the Commissioner of Food and Drugs or the Commissioner's designee; and~~

(IV) an opportunity for written appeal to—

(aa) the Commissioner of Food and Drugs; or

(bb) a designee of the commissioner who has not participated in the proposed withdrawal of approval (other than a meeting pursuant to subclause (III)) and is not a subordinate of an individual (other than the Commissioner) who participated in such proposed withdrawal;

(i) providing an opportunity for public comment on the notice proposing to withdraw approval no longer than thirty days;

(ii) ~~the publication of a summary of the public comments received, and the Secretary's response to such comments, on the website of the Food and Drug Administration; and~~

(iii) may include, at the Secretary's discretion, convening and consulting an advisory committee on issues related to the proposed withdrawal~~, if requested by the sponsor and if no such advisory committee has previously advised the Secretary on such issues with respect to the withdrawal of the product prior to the sponsor's request.~~

Justification: Providing sponsors with opportunities to meet with the FDA Commissioner, to have a public comment period requiring that FDA responds to all submitted comments, and to request advisory committee before withdrawing an unproven accelerated approval drug unnecessarily heightens the risks that patients may face medical or financial harms from these drugs. Removing procedures that cause undue delay to FDA withdrawal of proven accelerated approval drugs ensures that the agency is able to move with haste to protect patients when a therapy proves ineffective.