U.S. FOOD & DRUG ADMINISTRATION

Jianyi Zhang MD, PhD, MS
(b) (6) [redacted]

April 11, 2024

Re: Docket No. FDA-2022-P-2516

Dear Dr. Zhang:

This letter responds to the citizen petition (Amended Petition) that you submitted to the Food and Drug Administration (FDA or Agency), received on February 21, 2023, that amended the citizen petition received on October 12, 2022. The Amended Petition requests that FDA:

(1) Approve combined "Potential Therapeutic Drugs (PTDs)" intended to treat patients with Alzheimer's disease and those "patients with medical conditions currently without any effective medication" with only a demonstration of safety and "without any pre-market studies"; and

(2) Amend relevant regulations to allow combined "PTDs" "to treat patients with medical conditions currently without any effective medication" with only a demonstration of safety.[1]

We have carefully considered the information submitted in the Amended Petition. For the reasons stated below, the Amended Petition is denied.

I. BACKGROUND

A. Legal Requirements for Approval of Drugs

FDA's regulation of drug products is governed by the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C 301 et seq.) and the Agency's implementing regulations codified in Title 21 of the Code of Federal Regulations (CFR). The FD&C Act makes it unlawful to introduce into interstate commerce a new drug without first obtaining FDA approval of a new drug application (NDA) or abbreviated new drug application.[2] Before approving an application, FDA

[1] Amended Petition at 1.
[2] Section 505(a) of the FD&C Act (21 U.S.C. 355(a)); see also section 301(d) of the FD&C Act (21 U.S.C. 331(d)) (prohibiting the marketing of any article in violation of section 505 of the FD&C Act).

must determine that the drug product is both safe and effective for use under the conditions prescribed, recommended, or suggested in the drug product's proposed labeling.[3]

The statutory standard for determining whether a new drug is effective is "substantial evidence" derived from "adequate and well-controlled investigations" conducted by qualified experts, from which those experts could fairly and responsibly conclude that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in its labeling.[4]

FDA must deny marketing approval if, among other reasons, there is a lack of substantial evidence that the drug will have the effect it purports or is represented to have, the results of safety testing fail to show that the drug is safe, or on the basis of any other information before the Agency, there is insufficient evidence to determine whether the drug is safe for use under the conditions prescribed, recommended, or suggested in the labeling.[5]

B. The Amended Petition

In your Amended Petition, you request that FDA approve what you have termed "Potential Therapeutic Drugs (PTDs)" intended to treat patients with Alzheimer's disease and those "patients with medical conditions currently without any effective medication" with only a demonstration of safety and "without any pre-market studies."[6] The Amended Petition uses the term *PTD* to refer to "new compound entities"[7] that "might be essential or potentially play a vital role in treating certain medical conditions . . . if they are included in treatment regimens with similar compounds or biproducts."[8] We have interpreted this request to be for the approval of new drugs for use in combination with one another that you believe will be effective in treating Alzheimer's disease and "medical conditions currently without any effective medication" with only a demonstration of safety.[9] You also request that FDA "[a]mend relevant regulations to allow combined PTDs . . . to treat patients with medical conditions currently without any effective medication" with only a demonstration of safety.[10] The central contention of the Amended Petition is that the benefits of approving PTDs without a demonstration of effectiveness, and only evidence of safety, outweigh the risks of such a practice for PTDs for Alzheimer's disease and "patients with medical conditions currently without any effective medication."[11]

In support of your Amended Petition, you assert that developing drugs to treat these conditions is

[3] Sections 505(b)(1) and (d) of the FD&C Act (21 U.S.C. 355(b)(1) and (d)).
[4] Section 505(d) of the FD&C Act. The characteristics of adequate and well-controlled studies are set forth in FDA regulations at 21 CFR 314.126.
[5] Sections 505(d)(2), (d)(4), and (d)(5) of the FD&C Act.
[6] Amended Petition at 1.
[7] The Amended Petition uses *new compound entity* and *NCE* in the place of new drug. We believe that the intended use of *new compound entity* in the Amended Petition is interchangeable with new drug. Therefore, in this response, we use new drug instead of *NCE*.
[8] Amended Petition at 2.
[9] Id. at 1.
[10] Id.
[11] Id.

lengthy and costly.[12] The Amended Petition contends that if PTDs were allowed on the market without demonstration of efficacy, clinicians would be able to quickly discern (in a few weeks or months) whether a particular combination of drugs would be effective in specific circumstances.[13] Additionally, you contend that PTDs do not present increased risks compared to other drugs on the market because "all approved drugs are only required to show safety compared with controls by themselves and are not required to be safe when others are present."[14] The Amended Petition also states that PTDs approved without demonstrating efficacy "would not expose patients to an unreasonable and significant risk of illness or injury" and that the benefit of approving, by a demonstration of safety only, PTDs that are intended to treat Alzheimer's disease and medical conditions currently without any effective medication outweighs the risks.[15] Finally, you assert that FDA's approval of Leqembi (lecanemab-irmb) under BLA 761269 on January 6, 2023, with an indication for the treatment of Alzheimer's disease, should not affect FDA's openness to alternative treatments for Alzheimer's disease.[16]

II. DISCUSSION

FDA denies the actions requested in your Petition because, as discussed below, such actions would be inconsistent with federal law. Such actions also would not be scientifically sound.

FDA lacks legal authority to grant your request to approve "PTDs"—or any new drugs, including those proposed for use in combination with other drugs—without a demonstration that the drugs meet the statutory standard for effectiveness under their proposed conditions of use. Similarly, FDA lacks legal authority to grant your request to amend FDA's regulations to provide for approvals of "PTDs," or any drug products, without the showing of effectiveness required under the FD&C Act. These actions would directly conflict with Federal law. As discussed above, the FD&C Act requires that before approving an application, FDA must determine that the drug product is both safe and effective for use under the conditions prescribed, recommended, or suggested in the drug product's proposed labeling.[17] Thus, for a drug to be approved, whether for use by itself or for use in combination with another drug, the application must demonstrate that the drug product is both safe and effective for that use.

You argue that because there are "[d]iseases that can only be effectively treated with two or more [NCEs] together or much better treated by their combinations, but not individually"[18] such drugs should "go onto the market," without a demonstration to FDA of effectiveness, "with clinical indications."[19] Although you acknowledge the statutory requirement "that a compound must [be] show[n] [to be] safe and eff[ective] in clinical trials," you argue that "a combination of PTDs is not a compound, but more than a (one) compound," and that there is "no clause to require any combination to [be] show[n] [to be] effective and safe in clinical trials."[20] Your assertion that a

[12] Id.
[13] Id. at 2.
[14] Id. at 4.
[15] Id.
[16] Id. Leqembi's approval was converted from accelerated to traditional approval on July 6, 2023.
[17] Sections 505(b)(1) and (d) of the FD&C Act (21 U.S.C. 355(b)(1) and (d)).
[18] Amended Petition at 2.
[19] Amended Petition at 2.
[20] Amended Petition at 4.

drug intended for use in combination with another drug for a "clinical indication" is not required to meet statutory standards for both safety and effectiveness is incorrect.

To obtain approval of a new drug, the applicant must submit to FDA an application that includes, among other things, "full reports of investigations which have been made to show whether such drug is safe for [the proposed] use and whether such drug is effective in [that] use."[21] Pursuant to section 505(d)(5) of the FD&C Act, if FDA finds, "on the basis of the information submitted to [FDA] as part of the application and any other information before [FDA] with respect to such drug, there is a lack of substantial evidence that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the proposed labeling thereof," FDA must refuse to approve the application.[22] As described above, the FD&C Act defines "substantial evidence" to mean "evidence consisting of adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved, on the basis of which it could fairly and responsibly be concluded by such experts that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the proposed labeling thereof."[23]

Accordingly, if an applicant intends to market a new drug with the conditions of use described in your Petition—for use in combination with another drug to treat Alzheimer's disease, or another "clinical indication"—the applicant must submit to FDA an application that includes data and information, based on adequate and well-controlled investigations, including clinical investigations, showing that the drug is effective for such conditions of use.[24] If FDA does not find that those data and information provide substantial evidence of the drug's effectiveness when used in combination with the other drug for treatment of Alzheimer's disease, or for any other conditions of use proposed in the application, FDA must refuse to approve the application.[25]

Therefore, your requested actions to approve certain new drugs for use in combination with other drugs without a demonstration of effectiveness, and to amend FDA's regulations to allow for such approvals, would violate section 505 of the FD&C Act.

In addition, as a scientific matter, we disagree with the central premise of the Amended Petition that a demonstration of effectiveness is not necessary for PTDs. Specifically, we disagree that, in the absence of preapproval effectiveness data, PTD effectiveness could quickly be gleaned from clinical experience.[26] Reliance on clinicians to quickly discern "in a few weeks or months" whether a particular combination of drugs would be effective, as asserted in the Amended Petition, is not an evidence-based approach to determine effectiveness. Rather, reliance on

[21] Sections 505(b) and (d) of the FD&C Act (21 U.S.C. 355(b)(1) and (d)).
[22] Section 505(d) of the FD&C Act.
[23] Id.
[24] See sections 505(b) and 505(d) of the FD&C Act.
[25] See section 505(d)(5) of the FD&C Act. Section 505(d) also describes other circumstances in which FDA must refuse to approve an application.
[26] Amended Petition at 2.

clinical experience alone would be unscientific and anecdotal in nature and prone to inherent bias.

To establish a drug's effectiveness, it is essential to distinguish the effect of the drug "from other influences, such as spontaneous change in the course of the disease, placebo effect, or biased observation."[27] The FD&C Act requires that approval be based on adequate and well-controlled investigations, and FDA's regulations describe the characteristics of such investigations (e.g., design elements that are generally intended to minimize bias and permit a valid comparison with a control to provide a quantitative assessment of drug effect).[28] For example, in a clinical setting, patients might experience a placebo effect where the patient reports feeling beneficial effects of the combination therapy because of their awareness that their physician had prescribed the treatment for the underlying disease or condition. Similarly, a physician's awareness of the patient's treatment could also introduce bias (both known and unknown) into assessment methods. In contrast, randomized, double-blind, placebo-controlled trials,[29] where both the investigators and the subjects are not aware whether the subject is taking a particular tested therapy or placebo, minimize known and unknown sources of bias.

We also do not agree with the assertions in the Amended Petition that "PTDs," which you ask FDA to approve without a finding of effectiveness, present no increased risks compared to other drugs on the market and "would not expose patients to an unreasonable and significant risk of illness or injury."[30] A determination about a drug's safety is dependent on the specific conditions of use, including use in combination with another drug. With any combination of two or more active ingredients (whether they be previously approved drug products or NCEs), there is a possibility of unanticipated pharmacokinetic or pharmacodynamic interactions. Therefore, establishing the safety of an NCE by itself does not establish the safety of that NCE as used in combination with another drug.

Additionally, an FDA determination that a drug is *safe* is inextricably tied to an evaluation of that drug's effectiveness. Because all drugs have adverse effects, the demonstration of safety requires a showing that the benefits of the drug outweigh its risks under the conditions of use defined in labeling. Making an informed judgment that a drug has a favorable benefit-risk assessment requires determining that the drug's benefits, as well as its risks, are sufficiently characterized and that the benefits to the intended population will outweigh the risks if the drug product is approved. FDA considers the seriousness of the target condition, the drug's demonstration of effectiveness in that population, and other available treatments when weighing the drug's risks and benefits.[31] An evaluation of whether the risks to an intended population are acceptable requires an understanding of the degree to which the drug is effective in that population. FDA

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[27] 21 CFR 314.126(a).

[28] See Section 505(d) of the FD&C Act; 21 CFR 314.126(a); *See* also the draft guidance for industry *Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products* (December 2019). When final, this guidance will represent FDA's current thinking on this topic. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/regulatory-information/search-fda-guidance-documents.

[29] Alternative clinical trial designs may sometimes be proposed for investigating the efficacy of new investigational drugs. In most circumstances, such alternative clinical designs are less optimal than the use of randomized, double-blind clinical trials.

[30] Amended Petition at 2-4.

[31] See guidance for industry *Benefit-Risk Assessment for New Drug and Biological Products* (October 2023).

may be more likely to make a favorable benefit-risk determination for a drug with known risks if the drug is shown to be very effective in the intended population, especially if the drug is intended to treat a serious disease. Thus, establishing quantifiable benefit is crucial to determining whether a drug is safe and that the drug's benefits outweigh its risks.

Your Amended Petition states that "PTDs cannot pass the currently approved process into the market."[32] However, many drug products have been approved and labeled for use in combination with other drug products and can be legally marketed.[33] Additionally, in 2013, in recognition of the promise that combination therapy offers as an important treatment modality in many disease settings, including cancer, cardiovascular disease, and infectious diseases, FDA issued the guidance for industry, *Codevelopment of Two or More New Investigational Drugs for Use in Combination*.[34] The guidance is intended to assist sponsors in the codevelopment of two or more new investigational drugs that have not been previously developed for any indication to be used in combination to treat a disease or condition. The guidance describes a high-level, generally applicable approach to codevelopment of new investigational drugs for use in combination, describes considerations for determining when codevelopment is an appropriate option, makes recommendations about nonclinical and clinical development strategies, and addresses certain regulatory process issues.[35]

The Amended Petition also discusses FDA's approval of Leqembi and states that this approval should not affect FDA's openness to alternative treatments for Alzheimer's disease.[36] FDA's approval of Leqembi does not diminish FDA's openness to alternative treatments for Alzheimer's disease. The Agency welcomes submission of alternative treatments for the treatment of Alzheimer's disease and will review any such applications for safety and effectiveness in accordance with applicable statutory and regulatory requirements.

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[32] Amended Petition at 2.

[33] *See, e.g.*, nivolumab in combination with ipilimumab for the treatment of melanoma, non-small cell lung cancer, malignant pleural mesothelioma, renal cell carcinoma, colorectal cancer, hepatocellular carcinoma, and esophageal cancer. Opdivo (nivolumab) prescribing information (revised October 2023), Sections 1.1, 1.4, 1.5, 1.6, 1.10, 1.11, and 1.12, available at https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/125554Orig1s121lbl.pdf; Yervoy (ipilimumab) prescribing information (revised February 2023), Sections 1.1, 1.3, 1.4, 1.5, 1.6, 1.7, and 1.8, available at https://www.accessdata.fda.gov/drugsatfda_docs/label/2011/125377s0000lbl.pdf. *See also* esketamine hydrochloride in conjunction with an oral antidepressant for the treatment of treatment-resistant depression in adults and depressive symptoms in adults with major depressive disorder with acute suicidal ideation or behavior. Spravato (esketamine) nasal spray prescribing information (revised October 2023), Section 1, available at https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/211243s012lbl.pdf.

[34] Guidance for industry *Codevelopment of Two or More New Investigational Drugs for Use in Combination* (June 2013).

[35] Id.

[36] Amended Petition at 3.

III. CONCLUSION

For the reasons explained above, your Amended Petition is denied.

Sincerely,

Douglas C. Throckmorton -S

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