Citizen Petition

This petition for administrative action is submitted by Jianyi Zhang (petitioner) pursuant to 21 C.F.R. § 10.30 and relevant provisions of the Federal Food, Drug, and Cosmetic Act or the Public Health Service Act to request that the Commissioner of Food and Drugs (the "Commissioner") to issue approval of using combined Potential Therapeutic Drugs (PTDs) to treat Alzheimer's disease.

A. ACTION REQUESTED

(1) To issue approval of using combined Potential Therapeutic Drugs (PTDs) that all only pass the safety tests to treat patients with Alzheimer's disease without any pre-market studies. (2) To issue approval of using combined PTDs that all only pass the safety tests to treat patients with medical conditions currently without any effective medication. (3) Amend relevant regulations to allow combined PTDs that only pass the safety tests to treat patients with medical conditions currently without any effective medication.

B. STATEMENT OF GROUNDS

(1) Approval of drug products in the U.S. is governed by a rigorous review process regulated by the Food and Drug Administration (FDA). The 1938 Federal Food, Drug, and Cosmetic Act (FDCA) established the safety requirement for new drug products. A 1962 amendment to the FDCA additionally requires that a drug shown to be effective through "substantial evidence" derived from "adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the involved" (FDCA, Section 505 (d)).

(2) Successfully developing a drug through a new compound entity (NCE) is very costly and time-consuming; it takes roughly 10-15 years and over 3 billion dollars on average. The prohibitive cost of the process makes developing a new drug with multiple NCEs impossible.

Conceptually, according to drug treatment, diseases may be roughly divided into three types:

(a) Diseases can be treated effectively with a single drug

Some diseases can be cured with a single medication. For example, Escherichia coli causes urinary tract infections, Staphylococcus aureus can cause lobar pneumonia, and both could be treated successfully with single antibiotics before the occurrence of drug-resistant strains.

(b). Diseases can be treated effectively by different drugs separately and more effectively by combining other drugs.

Different drugs may have a synergistic effect. Hypertension, diabetes, AIDS, asthma, and gastric ulcers belong to this category. There are eight types of medications to treat hypertension; taking several drugs together can produce a more substantial antihypertensive effect. Each drug in the cocktail recipes for AIDS treatment and gastric ulcers is an approved medication on the market.

(c). Diseases that can only be effectively treated with two or more New Compound Entities (NCEs) together or much better treated by their combinations, but not individually.

(4) It is known that quite a few NCEs only pass the safety test but do not show efficacy in the trial. This type of NCE might be essential or potentially play a vital role in treating certain medical conditions only if they are included in treatment regimens with similar compounds or bioproducts. Ones could call them Potential Therapeutic Drugs (PTDs). PTDs cannot pass the currently approved process into the market.

(5) Alzheimer's disease (A.D.) is a devastating neurological disorder. The World Alzheimer Report 2015 revealed that 46.8 million people worldwide were living with dementia in 2015, and the total global societal cost of dementia was estimated to be $818 billion U.S.D. A.D. is the most common dementia type and may account for 60–70% of dementia cases.

(6) Clinical trials select a compound from thousands of ones with a specific target. Dozens of compounds or bioproducts were "would-be" Alzheimer's drugs that failed the last phase of clinical trials for lack of efficacy. They aimed at different targets in the presumed pathogenesis process in Alzheimer's disease.

(7) PTDs are compounds tested in trials where safety is comparable to placebo. Combined PTDs do not increase their risks compared with other drugs on the market.

(8) One might argue that combined PTDs might have unpredictable side effects in the market, but this is true for any drug when approved.

(9) There is no PTD in the market nor data to tell us what combination is effective in what circumstances. If combined PTDs are on the market, the doctor would probably soon discern the proper conditions for indications of combined PTDs.

(10) The clinical impacts of PTDs can be demonstrated in a few weeks or months that might slow, stop, reverse the process of the illness, or even cure it.

(11) Pharmaceutical companies might have PTDs locked in their safe boxes without commercial benefit. It would benefit manufacturers significantly if PTDs could go onto the market with clinical indications.

(12) On January 6, 2023, FDA granted Leqembi (lecanemab-irmb), which should not reduce necessity for application of PTD.

(13) During the trial, about 20% of participants who received lecanemab showed abnormalities on their brain scans that indicated swelling or bleeding. More people might suffer from the condition with a larger population. If true, the company might decide to withdraw the drug from the market, it is a difficult for both the manufacturer or FDA to make the decision.

PTD does not require clinical trials, its cost would be much lower, and withdrawal of any PTD will have a little loss for manufacturers.

(14) Eisai (a pharmaceutical sponsor) estimates that the drug costs $26,500 annually per person per year, while the average social security per person is only around $16,000 per year. Medicare only covers a fraction of the cost. This medicine is simply unaffordable for most people, for them it does not exist. However, PTD has no further research expense. If successful, the price will be greatly reduced, which could be a few percent of the cost with the approved drug.

(15) In the reports, Leqembi is only 27 % effective to improve cognitive funtion, whereas PTDs can have unlimited combinations, which may provide effective combinations and the effect could be much higher.

(16) Finding a drug with more efficacy and lower price is a non-stop process. Even if the drug is successful to some extent, there are still many other compounds for treatment in Alzheimer's pipeline, which should not be terminated just because of one with a moderate success and lots of uncertainties. The same principle also applies to PTDs.

(17) PTDs in the market are a five-wins situation for pharmaceutical companies, doctors, patients, families and governments.

(18) President Roosevelt articulated his vision for a postwar world founded on four fundamental human freedoms: freedom of speech, freedom of worship, freedom from want, and freedom from fear, which set the basis of human rights.

(19) Approximately 10% of Americans over 65 suffer from A.D., and 5 million have mild cognitive symptoms. Persons who have some of the symptoms might have a fear of suffering from A.D. in the coming years. Combined PTDs have unlimited potential to control the process, which will comfort them with hopes, with much more freedom from fear.

(20) Allowing combined PTDs in the market is not only a regulatory issue but a human right that affects millions of Americans.

(21) Pursuant to 21 U.S. Code § 360bbb-3 (c) (7):

in the case of immediately life-threatening diseases, the available scientific evidence, taken as a whole, provides a reasonable basis to conclude that the investigational drug or investigational device may be effective for its intended use and would not expose patients to an unreasonable and significant risk of illness or injury.

(22) In the U.S., official death certificates recorded 121,499 deaths from A.D. in 2019; over 10,000 persons died each month with A.D. For a few dozen thousand people who might die in the coming months due to the medical condition, A.D. is a chronic disease, some of patients is in immediately life-threatening condition, many of them is in a process to be in life-threatening situation. Combined PTDs have the potential to save their lives.

(23) Treating patients with combined PTDs does not lower safety requirement by the FDA, as 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.

(24) Treating patients with combined PTDs does not lower the efficacy criteria set by FDA, which requires that a compound must show safe and efficacy in clinical trials; however, a combination of PTDs is not a compound, but more than a (one) compound, the regulation has no clause to require any combination to show effective and safe in clinical trials.

(25) Ms. Joy Lee sent an email to respond to my letter to the Commissioner sent last September, she did not provide any reason why PTDs should not be applied, which defaults PTDs' rationality and feasibility.

(26) In clinical trials, a PTD have similar profiles of side-effects as a placebo; side-effects of a combination of a couple or a few PTDs are similar to ones of placeboes, or sugar pills, which would not expose patients to an unreasonable and significant risk of illness or injury, thus, the benefits significantly overweight the risks.

(27) The FDA has jurisdiction and responsibility to approve the usage of combined PTDs without any further pre-market trials.

C. ENVIRONMENTAL IMPACT

PTDs could be claimed for categorical exclusion under §§25.30, 25.31, 25.32, 25.33, or §25.34 of this chapter or an environmental assessment under§25.40 of this chapter.

D. ECONOMIC IMPACT

(a) Cost increases to industry, government, and consumers: cost will decrease to industry, government, and consumers as no additional and costly clinical trials need to be done.

(b) Productivity of wage earners, businesses, or government: combined PTDs will make non-profit products into profitable ones with tremendous increased productivity.

(c) Competition: even in the future, if one discovers a single compound or bioproduct safe and effective, combined PTDs could still be a more effective and economical way to treat the illness with broader indications.

(d) Supplies of essential materials, products, or services: there is a minimal impact of the issue.

(e) Employment: PTDs in the market will promote employment.

(f) Energy supply or demand: there is no impact of the issue.

E. CERTIFICATION

The undersigned certifies that, to the best knowledge and belief of the undersigned, this petition includes all information and views on which the petition relies and that it includes representative data and information known to the petitioner which are unfavorable to the petition.

Respectfully submitted

Signature,

Amended on 2/17/2023.

Jiang, Zhang