December 23, 2020

Electronic Submission

Division of Dockets Management
Food and Drug Administration
Department of Health and Human Services
5630 Fishers Lane, Room 1061
Rockville, MD 20852

CITIZEN PETITION

This petition is submitted to the U.S. Food and Drug Administration (FDA) under 21 C.F.R. 10.30 by Meg D. Newman, MD.

I. INTRODUCTION

In my petition I am writing from the perspective of both a **physician clinician-educator** (UCSF Emeritus-Department of Medicine) and a **medical patient** who has suffered 18 total episodes of acute and/or recurrent *C. difficile* infection (CDI). During my last episode of CDI, I was hospitalized with sepsis and required months to recover. My CDI is now cured but only because I was able to access microbiome-based therapies.

That being said, CDI is still one of the most urgent antibiotic-resistant bacterial threats in the U.S. and the most common healthcare-associated infection according to the CDC.[1] It is estimated that more than 450,000 individuals suffer from CDI each year in the U.S., with approximately 29,000 attributable deaths.[2] Standard-of-care antibiotics are often ineffective for recurrent CDI, with approximately 45% of patients experiencing another CDI recurrence following treatment of their first recurrence with standard-of-care antibiotics.[3] The morbidity of these recurrences to patients and their families is high. Patients suffer chronic diarrhea, profound weight loss, pain and malaise that often impairs a patient's ability to work (inside and/or outside the home) for weeks to months. There are currently zero FDA-approved drugs that address the underlying cause of recurrent CDI (disruption of the gut microbiome). This unmet need requires the **FDA's urgent attention especially because this can be rectified.**

[1] U.S. Centers for Disease Control and Prevention. Antibiotic Resistance Threats in the United States 2019. December 2019.

[2] Lessa et al. Burden of Clostridium difficile Infection in the United States. The New England Journal of Medicine 2015.

[3] Kelly. Can we identify patients at high risk of recurrent Clostridium difficile infection? Clin Microbiol Infect 2012.

Three companies recently reported positive efficacy and safety data from randomized, placebo-controlled, multi-center trials evaluating live microbiome-based drugs for the prevention of recurrent CDI.[4,5,6] Before these drugs can be brought to patients, there is a possibility that the FDA will require yet more placebo-controlled trials which would be an accelerant to **patient morbidity and mortality and unnecessary suffering for families.** The data provided by the three companies is **robust for efficacy and safety and justify immediate use.** Requiring additional placebo-controlled studies at this juncture, before these therapies are made available, will only create unnecessary suffering and death. In treating patients with recurrent CDI, I do not have the equipoise to accept another placebo-controlled trial for myself or to recommend one for my patients. My request is that the FDA focus on the success and safety of the data with live microbiome-based drugs for the prevention of recurrent CDI.

II. ACTIONS REQUESTED

A. I request that the FDA consider the data already collected for live microbiome-based treatments for the prevention of recurrent CDI to be sufficient for considering these products for approval.
B. I request that the FDA refrain from requiring additional placebo-controlled trials of live microbiome-based treatments for the prevention of recurrent CDI.

III. STATEMENT OF GROUNDS

1. The FDA needs to mitigate the morbidity and mortality from recurrent CDI. A careful review of the literature illustrates the robust safety and efficacy of live microbiome-based treatments.
2. Live microbiome-based treatments are the appropriate way to treat recurrent CDI and asking patients to be randomized to placebo is condemning them to a failing treatments.
3. Three companies recently reported positive efficacy and safety data from randomized, placebo-controlled, multi-center trials evaluating live microbiome-based drugs for the prevention of recurrent CDI.[4,5,6] The mechanism of action of all three therapies which reported positive results is well-known, supporting the position that additional placebo-

[4] Ferring. Rebiotix And Ferring Announce World's First with Positive Preliminary Pivotal Phase 3 Data for Investigational Microbiome-Based Therapy RBX2660. May 2020. https://www.rebiotix.com/news-media/press-releases/rebiotix-announces-worlds-first-positive-pivotal-phase-3-data-investigational-microbiome-based-therapy-rbx2660/

[5] Finch Therapeutics. Finch Therapeutics Announces Positive Topline Results from Randomized Controlled Trial of CP101, an Oral Microbiome Drug, for the Prevention of Recurrent C. difficile Infection. June 2020. https://finchtherapeutics.com/blog/finch-therapeutics-announces-positive-topline-results-from-randomized-controlled-trial-of-cp101-an-oral-microbiome-drug-for-the-prevention-of-recurrent-cdiff

[6] Seres Therapeutics. Seres Therapeutics Announces Positive Topline Results from Ser-109 Phase 3 Ecospor III Study in Recurrent C. Difficile Infection. August 2020. https://ir.seresTherapeutics.com/news-releases/news-release-details/seres-therapeutics-announces-positive-topline-results-ser-109

controlled trials are not necessary to establish efficacy and safety. Additionally, there is ample evidence from fecal microbiota transplantation (FMT) studies, including one randomized, placebo-controlled trial, that restoring microbiome diversity is a remarkably safe and effective approach for recurrent CDI.[7, 8]

4. The FDA has the essential role of making live microbiome-based drugs available and this is supported by the patients and the current literature.
5. Researchers consider placebo-controlled trials ethical only when there is clinical equipoise, i.e., the genuine uncertainty that one treatment is superior to another. As described recently by Kelly and Kahn, "internationally accepted guidelines support the use of a placebo only in specific circumstances: when there is no proven effective treatment for the condition under study, when withholding treatment poses negligible risk to patients, when there are compelling methodological reasons to use a placebo, or when the trial does not require participants to forgo treatment they would otherwise receive."[9] None of these criteria apply to the evaluation of live microbiome-based drugs for the prevention of recurrent CDI, and therefore additional placebo-controlled trials should be not be required.

IV. CONCLUSION

Recurrent CDI remains a threatening disease with significant mortality and morbidity for both patients and families. The incident numbers do not capture the short and long-term sequalae for individuals suffering with this condition or length of time that family and work life are disrupted for a patient suffering with recurrent CDI. At this juncture, we are fortunate to have robust data supporting both efficacy and safety for live microbiome-based treatments for recurrent CDI. Data which is elegant and strong enough in both the parameters of efficacy and safety to obviate the necessity of performing additional placebo-controlled trials for microbiome-based treatments. It is critical that FDA recognize and respect what we have learned from the existing body of literature and ensure that patients **have access to the most effective and safe treatment for recurrent CDI.** As both a physician and a patient who has suffered with CDI, I could not encourage a patient to accept a placebo-controlled trial given what we know, nor would I consent to that treatment for myself if the case where to arise.

V. OTHER REQUIRED INFORMATION FOR FILING OF CITIZEN PETITION

A. <u>Environmental Impact</u>

---

[7] Kelly et al. Effect of Fecal Microbiota Transplantation on Recurrence in Multiply Recurrent Clostridium difficile Infection: A Randomized Trial. Annals of Internal Medicine 2016.

[8] Van Nood et al. Duodenal Infusion of Donor Feces for Recurrent Clostridium difficile. New England Journal of Medicine 2013.

[9] Kelly and Khan. Is it ethical to conduct placebo-controlled trials of faecal microbiota transplantation for recurrent C. difficile infection? Lancet Gastroenterol Hepatol 2020.

The relief requested in this petition is categorically excluded under 21 C.F.R. 25.30 and therefore does not require an environmental assessment or an environmental impact statement.

B. Economic Impact

An economic impact statement will be submitted if requested by the Commissioner following review of this petition.

C. Certification

The undersigned certifies that, to the best of her knowledge and belief, 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.

Sincerely Yours,

Meg D. Newman, MD, FACP
UCSF Senate Emeritus-Medicine
Zuckerberg San Francisco General Hospital and Trauma Center

1484 16th Ave
San Francisco, CA
94122-3510

Ph: 415-509-1633