Ms. Carol J. Bennett
Deputy Director
Office of Regulatory Policy
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993

January 25, 2023

Re: Docket No. FDA-2020-P-2296

Dear Deputy Director Bennett:

This letter is in regard to the Citizens Petition (FDA-2020-P-2296) filed December 1, 2020, and the Agency's response dated May 27,2021, both herein attached.

Nearly two years have passed since the Petition was filed and the Agency responded that the Petition, *"raises complex issues requiring extensive review".* The Petitioner respectfully disagrees with the Agency's response and continued lack of action in implementing the recommendations of the Agency's own appointed advisory board on this matter. These recommendations directly correlate to this Citizens Petition which provides for enhancing the accuracy and standard of care for dosing single ingredient acetaminophen for pediatric patients 2-4 years of age.

The Petitioner urgently requests that the Agency take immediate action to comply with and implement the Agency's own appointed advisory board's dosing recommendations; and to judiciously enforce Sec. 502(a) [21 U.S.C. 352] of the U.S. Federal Food and Cosmetic Act as it pertains to single ingredient Infant's acetaminophen product for 2-3 years of age that bears confusing and mis-leading directions.

For over a decade the Agency has ignored repeated advisory board recommendations designed to enhance dosing accuracy by firstly adopting a weight-based dosing schedule for the product. Conversely, at the same time the Agency continued to published dozens of industry guidance documents, including improving prescription container labels for acetaminophen-containing medicines, and limiting of the use of acetaminophen products, among others. Notwithstanding, and contrary to decades of published clinical studies, including one of the largest clinical studies supporting the approval of acetaminophen for the pediatric population, it appears the Agency finds providing an option of enhancing optimal dosing accuracy for infants, unimportant.

The Petitioner fails to see the complexity in revising the TFM to include a dose by weight method, particularly after the Agency itself and other worldwide health agencies recognize this as the most accurate mechanism of dosing this medication. Such a simplistic revision would only harmonize and provide the exact dosing mode pursuant to the directions of currently sold single ingredient acetaminophen Infants product for 2-3 years of age.

Moreover, the commercial Infants single ingredient acetaminophen for 2-3 years of age product sold throughout the United States, bears confusing and misleading instructions reciting; "*if possible, use weight to dose, otherwise use age."* There is no dosing mechanism whatsoever to accomplish either dosing directions, the product provides solely for a set dose of 5 mL for all pediatric patients from 2-3 years of age or 24-35 lbs.

I provide for your convenience some key elements surrounding what should be considered a straightforward enhancement of dosing accuracy, patient safety and caregiver convenience while preparing and administering one of the most commonly used pediatric medications.

1) For almost four decades, dozens of studies corroborate the safety and efficacy of acetaminophen for use in pediatrics. The data demonstrated in those studies highlight that for an antipyretic dose to be achieved, a minimum dose of 10 mg/kg should be administered.

2) These studies also included the Boston University Fever Study that took place during 1991-to-1993, which is regarded as one of the largest pediatric drug trials ever conducted. This practitioner-based randomized clinical trial involved over twenty thousand children and was conducted at a dose of 12 mg/kg of acetaminophen.

3) Multiple large scale clinical trials have continued to demonstrate the effectiveness of a dose between this range; including within 12 unpublished clinical trials of 560 children receiving doses between 10-15 mg/kg, with average dose of 12.5 mg/kg, as submitted by Dr. Temple to the FDA in 2009, (submission to the Docket FDA-2009-N-0138 Liver injury Related to the Use of Acetaminophen.

4) On January 13, 1995, a Nonprescription Drugs Advisory Committee Meeting was convened by the FDA to discuss pediatric dosing in general. The committee determined its preference for weight-based dosing over age, height/length, or body-surface area, based dosing. The committee also accepted the requirement for age-based dosing, providing for an additional dosing method should the weight of the child not be known at the time of dosing. It was concluded at this meeting that pediatric dosing should be labeled by weight and by age, with the instructions to use weight for dosing, if known, and age if weight is not known.

5) On September 18, 1997, yet another committee was convened for the purpose to discuss dosing and labeling of OTC pediatric analgesic/antipyretic drug products. At this Nonprescription Drug and Arthritis Advisory Committee Meeting, the committee reiterated its preference of a primary weight-based dosing, but also recommended age-based dosing directions be additionally provided on the label.

6) During a May 17-18, 2011, of the FDA Joint Nonprescription Drugs Advisory Committee and Pediatric Advisory Committee, the panel voted unanimously that weight-based dosing directions be added to the existing age-based labeled dosing directions for children ages 2-12.

7) Over the past decade the U.S. FDA has continued to promote and publish guidance for the industry intended to limit and encourage the safer use and dosing of Acetaminophen.

8) Notwithstanding, commercially marketed and sold single-ingredient acetaminophen product for Infants 2-3 years of age provides for a set dose in the amount of 5 mL of Acetaminophen, even though its misleading and confusing directions state: ***"dose by weight, if possible, otherwise use age"***. There is no mechanism for dosing by weight nor age.

9) A set dose of 5 mL of the single-ingredient acetaminophen product for Infants 2-3 years of age (24-35 lb.) population, provides for highly variable dosing that may increase the prospect of a subtherapeutic or supratherapeutic dose due to dosing at the near extremes of a minimum therapeutic dose of 10 mg and maximum of 15 mg.

10) The Agency has consistently provided guidance and has held multiple meetings about limiting and providing higher accuracy of single-ingredient acetaminophen.

As of the date hereof, it remains unclear as to the adverse consequences that may have occurred due to the Agency's lack of intention and/or enforcement of this matter which affects millions of infants. The petitioner simply requests the Agency complies with its own appointed advisory board's recommendations as well enforce its own published regulations for this medication as marketed and sold within the United States.

Sincerely,

 - U.S. Department of Health and Human Services