Division of Dockets Management **April 24, 2024**
Food and Drug Administration
Department of Health and Human Service
5630 Fishers Lane, Room 1061
Rockville, MD 20857

CITIZEN PETITION

Dear Sir/Madam:

The undersigned hereby submits this Citizens Petition under 21 CFR § 10.30 and 10.20 requesting the Commissioner of Food and Drugs to publish a statement of enforcement expressly prohibiting the further use of misleading, confusing and inadequate directions for over-the counter (OTC) single-ingredient acetaminophen products for 2-3 year of age, 24-35 lb Infants.

1. Requested Action

Parenteral Technologies LLC (the "Petitioner") respectfully requests the United States Food and Drug Administration (the "FDA") to issue a notice of compliance and publish a statement of enforcement requiring the removal and further use of specific labeling and directions, explicitly; "***if possible, use weight to dose;"*** collectively hereinafter referred to as (the "Directions"), from all Infant's OTC single-ingredient acetaminophen liquid drug formulations for 2-3 year of age, 24-35 lb, hereinafter referred to as (the "Product").

2. Statement of Grounds

A) The Directions are misleading, confusing and are inadequate, thus should be removed or amended pursuant to; Section 502 of the Federal Food, Drug and Cosmetic Act (FD&C) 21 U.S.C. § 352– misbranded drugs and devices.

B) More specifically, the Directions are contrary to FD&C statutory requirements 21 U.S.C. § 352 (a) and 21 U.S.C. § 352 (f), in addition to 21 CFR § 201.5 of the Food and Drug Administration Department of Health and Human Service Subchapter C.

C) The Directions additionally are contrary to the format and content requirements for OTC drug product labeling under 21 CFR § 201.66 (a) 21 CFR § 201.66 (c) (6) of the Food and Drug Administration Department of Health and Human Service Subchapter C.

3. Background

Since the publication of the Tentative Final Monograph (the "TFM") in 1988, advancements in drug delivery and labeling for pediatric medications have demonstrated that unique pediatric dosing is necessary for reflecting the growth and maturational stages of pediatric patients. A scientific consensus of having pediatric patients dosed to personalized characteristic of weight and/or BSA has been widely regarded as the "gold standard" of pediatric dosing. This consensus of weight-based dosing was re-affirmed over decades, including by multiple FDA Advisory Committees, including a Pediatric Advisory Committee specifically convened to address the dosing of this Product. During this meeting, the Pediatric Advisory Committee voted unanimously that weight-based dosing directions should be added to the existing age-based labeled dosing directions for children ages 2-12 inclusive of this Product.[1]

Notwithstanding decades of FDA Advisory Committees recommendations, over 30 years later the TFM and Product are still absent any precise optimal dosing according to one or more personalized patient characteristics, including weight. In fact, the TFM remains in its antiquated form as published in 1988 directing the apportioning of tablets in unit form, yet complete obviating volume measurement (mL), which is the most common dosing form of the Product. Noteworthy, for over two decades the mL dosing method has been noticed in FDA guidance publications for the Product itself. Moreover, the current inclusion of weight-based dosing Directions on the Product (absent any meaningful mechanism other than to render the Product in conflict with statutory regulations), superficially seems have satisfied "the masses." That is with the exception of the 2–3-year-old infants and every parent and/or caregiver who are prejudiced against using a higher precision personalized dose - and rather are subject to use this rudimentary "just about" method of dosing.

Figure 1. Existing Federal Register, TFM, Children's Dosage Schedule for Acetaminophen

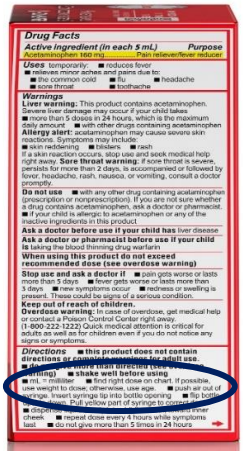
Age (Years)	Number of 80-mg or 81-mg dosage units	160 or 162 (mg)
Under 2……	Consult a doctor	
2 to under 4	2	160 or 162
4 to under 6	3	240 or 243
6 to under 9	4	320 or 324
9 to under 11	4 to 5	320 to 405

4. Product Labeling, Format, Content and Directions are Contrary to Regulations

Unequivocally, the Product and its Directions offer **one possible dose**, which is 5 mL for **all Infants** between 24-35 lbs and 2-3 years of age. Notwithstanding, the Directions instruct a caregiver to; "***if possible, use weight to dose.***"

Figure 2. Current Labeling and Directions of Product

Infant's OTC single-ingredient acetaminophen liquid drug formulations for 2-3 year of age, 24-35 lb



Weight (lb)	Age (yr)	Dose (mL)*
under 24	under 2 years	Ask a doctor
24-35	2-3 years	5 mL

- find right dose on chart. **If possible, use weight to dose** on chart otherwise use age.

A) The Product's labeling content and format do not conform to 21 CFR § 201.66 (a) of the Food and Drug Administration Department of Health and Human Service Subchapter C; as the TFM contains no dosing method for dosing by weight pursuant to the labeling displayed on the Product, ***"if possible, use weight to dose."***

B) The Product's directions do not conform to 21 CFR § 201.66 (c) (6) of the Food and Drug Administration Department of Health and Human Service Subchapter C; as the directions indicate and are labeled; ***"if possible, use weight to dose"*** which is not a recognized dosing method in the applicable OTC monograph, nor as published within the TMF for the intended Product.

C) The Product's labeling does not conform to the requirements of FD&C 21 U.S.C. § 352 (a); as the labeling comprise directions; ***"if possible, use weight to dose"*** which is not an applicable dosing method and as such is *"false or misleading in any particular"* and thus **deemed misbranded**.

D) The Product's directions do not conform to the requirements of FD&C 21 U.S.C. § 352 (f); as the directions comprise; ***"if possible, use weight to dose"*** which is not a possible dosing mechanism or applicable dosing method and as such, not "*adequate directions for use"* and thus **deemed misbranded**.

5. Product Labeling and Directions are Contrary to FDA Guidance for Industry

In May 2011, the FDA published Guidance for Industry for Dosage Delivery Devices for Orally Ingested OTC Liquid Drug Products, hereinafter (the "Guidance"). The Guidance introduction recites; *"This document is intended to provide guidance to firms that are manufacturing, marketing, or distributing orally ingested over-the-counter (OTC) liquid products that are packaged with dosage delivery devices (e.g., calibrated cups, droppers, syringes, spoons). Because written, printed, or graphic matter appearing on dosage delivery devices packaged with OTC liquid drug products is considering labeling, such marking on these devices must not be false or misleading and must be clear and consistent with the drug product's direction for use. (see sections 201(m), 502(a) and 502(f)(1) of the Federal Food, Drug and Cosmetic Act.)"* [2]

Moreover, the Guidance continues to cite section **FD&C 21 U.S.C. § 352 (a) and FD&C 21 U.S.C. § 352 (f)**, both reaffirming that a drug is considered misbranded if: a) its labeling is false or misleading in any particular [or]…f) it bears inadequate directions for use. The guidance further recites; *"in addition to misbranding under section 502(a) of the FD&C Act (21U.S.C. 352) (a), when dosage delivery devices packaged with OTC liquid drug products fail to bear a liquid measure mark or markings consistent with the labeled dosage directions, the products also lack adequate directions for use and are misbranded under section 502(f)(1) of the FD&C Act (21 U.S.C. 352(f)(1).* [2]

**** The Product and its dosage delivery device comprised within indisputably falls under the Guidance and statutory regulations herein.***

A) The Product's labeled dosage directions describe ***"if possible, use weight to dose"***, yet the dosage delivery device comprised with the Product provides no such *written, printed, or graphic matter* to allow such method of dosing the Product.

B) The dosage delivery device comprised with the Product does not provide any *written, printed, or graphic matter* that is *clear and consistent with the drug product's direction for use of;* ***"if possible, use weight to dose."***

- *When dosage delivery devices packaged with OTC liquid drug products fail to bear a liquid measure mark or markings consistent with the labeled dosage directions, the products also lack adequate directions for use and are misbranded under section 502(f)(1) of the FDC Act (21 U.S.C. 352(f)(1).* [2]
- *Because written, printed, or graphic matter appearing on dosage delivery devices packaged with OTC liquid drug products is considering labeling, such marking on these devices must not be false or misleading and must be clear and consistent with the drug product's direction for use. (see sections 201(m), 502(a) and 502(f)(1) of the Federal Food, Drug and Cosmetic Act.)"* [2]

6. Statutory Requirements and Regulatory History

On December 9, 1991, the FDA began to publish compliance notices to alert all drug establishments to review labeling for all drug products marketed with an accompanying dosage delivery device to determine if the product's labeling was compatible with the markings on the dosage device. The compliance notices further recited that any dosage delivery devices that had markings inconsistent with the product's labeling render the drug product misbranded under FD&C 21 U.S.C. § 352 (a). [2]

From November 1991 to January 1992 the FDA issued warning letters to five firms marketing OTC liquid drug products with dosage delivery products that were not compatible with the products' labeled dosage directions. Those letters cited violations of Section 502 of the FD&C 21 U.S.C. § 352 (a), because the markings on the dosage cups packaged with the products were misleading within the context of the labeled directions for use. [2]

The FDA also underscores within the Guidance, that; "*despite these efforts, through routine monitoring and surveillance programs, FDA is aware that an increasing number of orally ingested OTC liquid drug products are packaged with dosage delivery devices that are incompatible with labeled product dosage directions.*" [2]

7. Weight Base Dosing of Product - Regulatory Background

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.[3]

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. [4]

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. [5]

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 of discussing 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 FDA has continued to promote and publish guidance for the industry intended to limit and encourage the safer use and dosing of Acetaminophen. [2,6]

8) Notwithstanding, the commercially marketed Product has a set dose in the amount of 5 mL even though its directions, (although contrary to the Guidance and all statutory regulations), continue to state; ***"dose by weight, if possible"***, *see Figure 2.*

9) A set dose of 5 mL of the Product 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/kg and the maximum of 15 mg/kg.

10) The FDA has consistently provided guidance and has held multiple meetings about limiting and providing higher accuracy of single-ingredient acetaminophen, and the Product. [6]

8. Conclusion

As of the date hereof, the facts remain unclear as to the adverse consequences that may have occurred due to lack of attention to this matter and the decades of previous Citizen Petitions "shelved" regarding this Product. **This Citizen Petition should be expedited as it directly affects millions of vulnerable infants.**

The Petitioner simply requests that the FDA comply with its own appointed advisory board's recommendations, as well enforce its own published statutory regulations and requirements for this Product - as it would for any other medication under its control within the United States.

9. Environmental Impact:

This petition is categorically exempt from the requirements for an environmental assessment or an environmental impact statement pursuant to 21 C.F.R. §§ 25.30(h), (k) and 21 CFR 25.31 (a).

10. Economic Impact:

This information is only required if requested by the Commissioner after review of the petition.

11. 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.

Sincerely,

[redacted]

References:

1) United States Food and Drug Administration. Meeting of the Nonprescription Drugs Advisory Committee. May 17-18, 2011. https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/NonprescriptionDrugsAdvisoryCommittee/UCM264148.pdf

2) United States Food and Drug Administration. Guidance for Industry Dosage Delivery Devices for Orally Ingested OTC Liquid Drug Products. https://www.fda.gov/files/drugs/published/Dosage-Delivery-Devices-for-Orally-Ingested-OTC-Liquid-Drug-Products.pdf

3) Temple AR. Pediatric dosing of acetaminophen. Pediatr Pharmacol (New York). 1983;3(3-4):321-7. PMID: 6677877

4) Boston University Fever Study. 1994 http://www.bu.edu/slone/research/scor-network/

5) Temple, Comments Regarding the Labeling of Pediatric OTC Acetaminophen. FDA-2009-N-0138, Joint Meeting of the Drug Safety and Risk Committees, June 29 and 30, 2009

6) United States Food and Drug Administration. Over-the-Counter Pediatric Oral Liquid Drug Products Containing Acetaminophen Guidance for Industry https://www.fda.gov/media/89475/download