November 21, 2020

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

CITIZEN PETITION

Dear Sir/Madam:

The undersigned hereby submits this citizens petition under 21 CFR § 10.30 and 10.20 to request the Commissioner of Food and Drugs to amend the United States Food and Drug Administration Federal Register's Tentative Final Monograph for Over-the-Counter Internal Analgesic, Antipyretic and Antirheumatic Drug Products as published, November 16, 1988, (TFM).

1. Introduction

The goal of this citizens petition is to request the United States Food and Drug Administration (FDA) to amend and expand the single-ingredient acetaminophen OTC consumer children's dosage schedule and directions for the 2-4 year of age group, as published within the TFM. More specifically, it is the intention of the petitioner to highlight clinically established historical data and request the FDA to implement simplistic, but crucial dosing amendments to the TFM and initiate policy statements for enforcement and recommendations of the same.

The requested amendments to the TFM as described herein, enable enhanced dosing methods that provide a narrowed consistent dose of children's single-ingredient acetaminophen, in contrast to the variable dosing schedule commercially utilized and published within the TFM. In addition, these proposed amendments also provide for juxtaposed ancillary dosing indicia that correlate the predetermined dose to one or more known patient characteristic, thus providing for visual dose reverification.

The petitioner categorically does not endorse nor contest any clinical studies supporting the established dosage schedule as published within the TFM. Conversely, it is the intention of this petition to propose and illustrate multiple dosing modifications to the published TFM dosage schedule solely for the FDA's evaluation of recasting the TFM of 1988. Moreover, as herein illustrated, the proposed amendments enable an optimized amount of medication to be delivered to one or more known physical characteristics of a child; thus, enhancing dose consistency while continuing to comply with the established TFM dosage schedule.

The proposed amendments additionally provide for a dosing schedule that adheres more closely to the original safety and efficacy studies used to support the use of OTC single-ingredient acetaminophen within the pediatric population.

Since the publication of the TFM in 1988, advancements in drug delivery and labeling for pediatric medications demonstrate that unique pediatric dosing is necessary for reflecting the growth and maturational stages of pediatric patients. The absence within the TFM of a precise optimal dose according to one or more individual patient characteristics has stifled innovation for the advancement of safety, dosing accuracy, as well as overall user adherence to directions.

As illustrated herein, through expanding the existing dosage schedule and permitting additional dosing methods as requested within this petition for; A*) dosing to individualized patient weight; and, B) dosing to an oral suspension dosage unit; and, C) dosing to a drug potency correlated to a specific dosing unit(s) or patient characteristic(s)*, would enable and/or entice a caregiver to further narrow an optimized dose of the medication to one or more known physical characteristic(s) of a child and/or correlating dosing units, thereof.

2. Requested Action

Parenteral Technologies LLC, the author of this petition, respectfully requests the FDA amend the children's over-the-counter dosage schedule and directions of single-ingredient acetaminophen for the 2 to under 4 years of age group as published within the TFM, and as described and illustrated herein in Section 6, (Figure 17a & 17b). In addition, the petitioner requests the FDA publish a statement of enforcement policy expressly permitting manufacturers of children's OTC single-ingredient acetaminophen to include labeling on the product that provides for the amended and expanded directions for use.

3. Statement of Grounds

The Tentative Final Monograph for Internal Analgesic, Antipyretic and Antirheumatic Drug Products for Over-the Counter Use for Children's Single-ingredient Acetaminophen for 2 to under 4 years of age (Figure 1), does not; A) provide for a dose by individual patient weight method; nor, B) accurately provides for available children's dosage units; nor, C) provides for any dosing mechanism to taper or enhance the TFM dosage schedule of 160-162 mg, either by volume, potency or additionally to any specific patient characteristic, more specifically as further described herein below as; A, B, and C.

Figure 1. Published 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**

A) Weight Based Dosing

The existing TFM for single-ingredient acetaminophen has not been updated nor harmonized to reflect the FDA's Joint Nonprescription Drugs Advisory Committee and Pediatric Advisory Committee unanimous decision which recommends; that weight-based dosing directions be added to the existing age-based dosing labeled directions for children ages 2-12, with the preferred mode of dosing firstly by patient weight.[1]

B) Dosage Units

The existing TFM provides for a single-ingredient acetaminophen dosage unit apportioned from a children's 80 mg–81 mg solid dosage unit or from an adult 325 mg solid dosage unit. The existing TFM does not provide nor reflects any single-ingredient acetaminophen dosage unit in oral suspension form, nor; corresponding dosing unit in any volume, notably the most widely utilized dosage unit for children between 2-4 years of age.

C) Enhanced Drug Concentration Indicia

The existing TFM lacks any dosing methods for dosing in units of potency of single-ingredient children's acetaminophen, other than the set 160–162 mg for the 2-4 years of age group. Thus, this set dose restricts any user enhancement and tapering of the medication to any additionally known specificity of patient characteristic, such as an exact month of age and/or specific patient weight or any other method for a narrowed dosing unit of the medication's concentration of 160-162 mg, whatsoever.

4. Pharmacodynamic and Clinical Studies Background

Acetaminophen has been marketed in children's OTC elixir form since 1959 and is considered one of the most widely used analgesic antipyretics for children. A multitude of clinical studies for children's acetaminophen has shown it to have equivalent efficacy to other analgesic antipyretics.[2-5] However, those same studies, among others, conclude its efficacy is contingent on the administration of adequate doses.[6,7,10]

Original dosage schedules for the use of acetaminophen in the pediatric population were conducted through the extrapolation of adult data and the subsequent apportioning of adult doses and dosage schedules, fractionally according to pediatric age. This presented many inconsistencies in accurately administering the correct consistent doses for changing and substantial body mass differences of pediatric patients. In fact, early studies concluded that there are rather large differences in the absorption and metabolism of acetaminophen between age groups and that acetaminophen absorption may occur at a somewhat greater rate in children if syrup form is utilized.[7] More recently, the British National Formulary conducted studies to review age-based guidelines for the dosing of paracetamol. This study concluded underweight and overweight children are at risk of inappropriate paracetamol administration based upon the standard practiced age-based dosing instructions.[8]

Early studies of dosing of pediatric populations by weight and/or body surface area were shown to be a more accurate basis for calculating an optimal drug dose for individual children.[9] Unfortunately, in regards to children's OTC acetaminophen use, the practice was not implemented commercially for decades.

Subsequent dose to weight pharmacokinetic comparison studies conducted by Petersen et al [1978] compared three doses of 10mg/kg, 20mg/kg and 30mg/kg in regard to their antipyretic efficacy and plasma acetaminophen level. Peak plasma levels were 8.0 µg/mL for 10mg/kg, 18.6 µg/mL for 20mg/kg and 23.6 µg/mL for 30mg/ conclude peak temperature decline did not coincide with peak plasma levels, (Figure 2).

Figure 2. Antipyretic Efficacy and Plasma Acetaminophen Level

Dose	Peak plasma levels	Peak temperature decrement (Hours following administration)				
		2.0	3.0	4.0	5.0	6.0
10mg/kg	8.0 µg/mL					
20mg/kg	18.6 µg/mL					
30mg/kg	23.6 µg/mL					

In 1983, Dr. Anthony Temple published studies to support the pharmacodynamic importance of a weight-based dosing schedule of acetaminophen for pediatric weight ranges. The studies pharmacodynamic and antipyretic efficacy results highlight that a minimum dose of 10 mg/kg (and within a range of 10-15 mg/kg) is necessary for optimal antipyretic efficacy when given at 4 hours intervals,[10] (Figure 3).

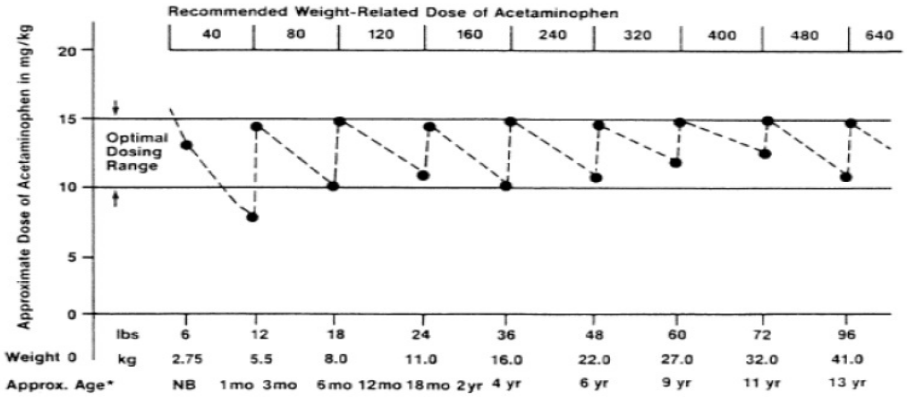
Figure 3. Comparison of Antipyretic Effect of Various Acetaminophen Doses[10]

Dose (mg/kg)	Initial temperature	Mean temperature decrement (°C) (Hours following administration)								Maximum decrement (°C)
		0.5	1.0	2.0	3.0	4.0	5.0	6.0	8.0	
5[a]	39.5	0.3	0.4	0.4	0.3	0.3	0.1	--	0.1	0.4
10[b]	39.5	0.3	0.8	1.5	1.6	1.4	1.1	1.2	0.9	1.6
20[c]	39.6	0.4	1.4	1.9	--	2.0	--	--	1.9	2.0

a) Windoffer and Vogel [1976]
b) Similar et al [1975. 1979]: Windorfer and Vogel [1976]; Peterson et al [1978]; Kienanen et al [1977].
C) Windorfer and Vogel [1976]; Peterson et al [1978].

Using composite data from these studies, Dr. Temple concluded that the data indicated that in order to produce a satisfactory temperature reduction for at least 4 hours, a minimum single dose of 10 mg/kg is necessary.[10] Dr. Temple summarizes pharmacodynamic assessments that conclude optimal temperature reduction may not occur with doses less than 10 mg/kg and pharmacokinetic assessments support dosing between 10-to-15 mg/kg range both in terms of single acute doses as well as repetitive doses for up to 2 or 3 days. This weight-based dosing schedule is still widely accepted and highlights the optimal dose range between a minimum of 10 mg/kg and a maximum of 15mg/kg.[10]

Figure 4. Dr. Anthony Temples Weight Based Dosing Schedule

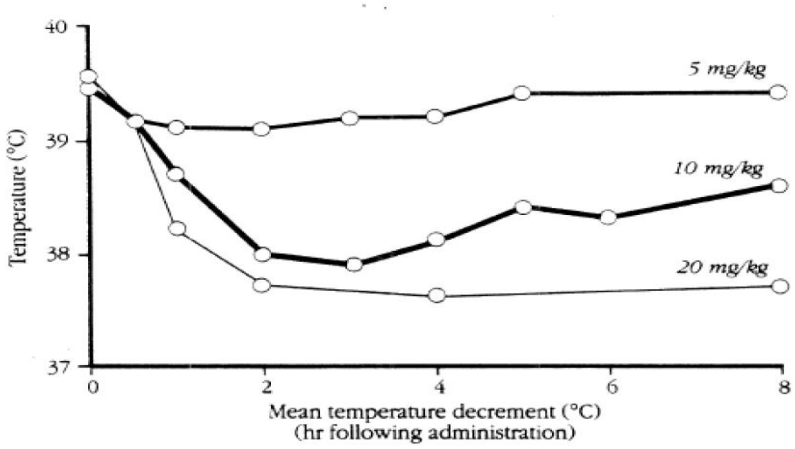


Temple, A.R., "Pediatric dosing of acetaminophen". Pediatric Pharmacology 1983; 3:321-327

For almost four decades, dozens of studies corroborate the safety and efficacy of acetaminophen for use in pediatrics when administered between a minimum dose of 10 mg/kg and a maximum of 15 mg/kg. These studies also included the Boston University Fever Study that took place from 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 via administering a 12 mg/kg dose of acetaminophen.[11] Since then, 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.[12]

In fact, Dr. Temple describes one of the earliest OTC mg/kg dosing schedules for pediatric acetaminophen was accomplished using a 80 mg children's tablet approved in 1970's and provided incremental doses of 40 or 80 mg for increasing weight or approximate weight ranges based on age. Moreover, Dr. Temple illustrates and recites a specific pediatric dosing schedule for acetaminophen which consisted of using more narrowly defined age ranges and importantly; specified weight ranges that provide a more consistent mg/kg dosing pattern which keeps the dose of acetaminophen within the 10-15 mg/kg range as published in 1983.[12] 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,[12] (Figure 5).

Figure 5. Comparison of antipyretic effects of three acetaminophen doses.[12]



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.

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.

During a May 17-18, 2011 meeting 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. [1]

Over four decades of pharmacokinetic data and efficacy studies have continued to support that a dose of 10 mg/kg produces an adequate antipyretic effect.[9,7,12,13]

Proposed Amendments to the Published TFM Dosage Schedule.

A) Dose Optimization to Specific Patient Weight

Some of the largest studies ever conducted to establish the safety and efficacy of single-ingredient acetaminophen for pediatric use were conducted pursuant to a specific potency (mg) dose of medication to an individual patient weight (kg).[2-7,10,12,13,16]

In fact, the literature that was prepared to review the antipyretic efficacy of acetaminophen for the FDA's Joint Nonprescription Drugs Advisory Committee and Pediatric Advisory Committee Meeting,[1] comprised 17 weight-based fever placebo and fever active controlled trials in Appendix 1. Only one trial was conducted with a dosing range of 10-15 mg/kg and the study concludes, "it was not designed to assess antipyretic efficacy."[1] The remainder of the trials were designed as a dose to individual patient specific weight (mg/kg).

The current weight-based dosing schedule as published by Dr. Temple[10] (and as commercially practiced), cannot be considered a dose by (patient) weight dosage schedule. This dosing schedule although designed as weight-based schedule, is a set-dose of 160 mg intended for all children within a predetermined range, either weight or age. Additionally, the commercially practiced dosing schedule, provides for a set dose of 160 mg of acetaminophen for all children within the range of 24 to 35 lb. or 24 to 36 months of age, comparable to the TFM set dose for all children within the 2-4 years of age range. There are no other dosing methods for administrating the medication to an individual patient weight and/or specific age, whatsoever.

Notwithstanding, this weight-based schedule of dosing children between this optimal dosing range has been shown extremely effective over decades. In the author's opinion the dosing schedule developed by Dr. Anthony Temple advanced the safety, efficacy, and convenience for generations of caregivers administering acetaminophen. It is however a dosing schedule that can be further enhanced, rather significantly, through very simplistic amendments.

The Temple weight-based schedule was developed to keep the dose within the "area" of optimal dosing, which was defined between 10–15 mg/kg,[10] Figure 6. However, the variation of the dose delivered within this weight-based schedule provides the near lowest antipyretic dose of 10 mg/kg and the near maximum dose of 15 mg/kg to the same children within the patient range, Figure 7.[10]

Figure 6.

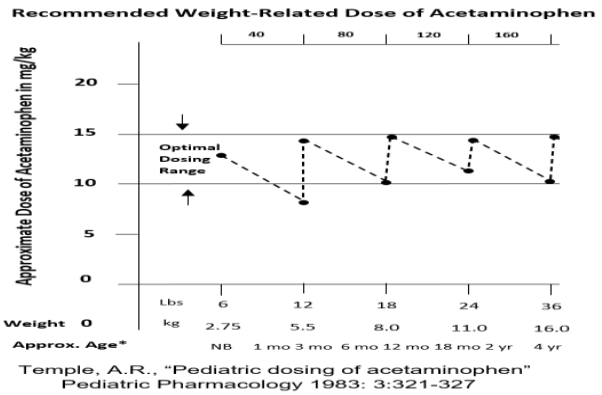


Figure 7.

LOWER LIMIT DOSE			
11 lb	4.99 Kg	(40 mg)	8.02 mg/kg
17 lb	7.71 Kg	(80 mg)	10.38 mg/kg
35 lb	15.88 Kg	(160 mg)	10.07 mg/kg
HIGHER LIMIT DOSE			
6 lb	2.72 Kg	(40 mg)	14.71 mg/kg
12 lb	5.44 Kg	(80 mg)	14.70 mg/kg
18 lb	8.16 Kg	(120 mg)	14.70 mg/kg
24 lb	10.89 Kg	(160 mg)	14.69 mg/kg

The current weight-based dosage schedule (although developed to provide consistent dosing), delivers a highly variable dose of +/- 40% difference to vulnerable small-mass children within the subject weight range, (Figure 6). Additionally, the dosage schedule provides doses near the minimum and maximum dosing limits, (Figure 7); thus, creating a narrow margin of error between an appropriate dose or the administration of a subtherapeutic or supratherapeutic dose.

While the safety and efficacy between a minimum dose of 10 mg and a maximum dose of 15 mg per kilogram has been well established, decades of studies also have identified that the dosing accuracy and adherence to this dosing schedule has not been without major challenges. In fact, perhaps one of the most recent disturbing studies concluded that 84.4% of parents made dosing errors while administering OTC oral elixirs.[14] While certainly the most publicized and serious reported errors may be overdosing, perhaps a more common error as other studies have concluded, "underdosing of acetaminophen by parents is a more common phenomenon than over dosing."[15,16]

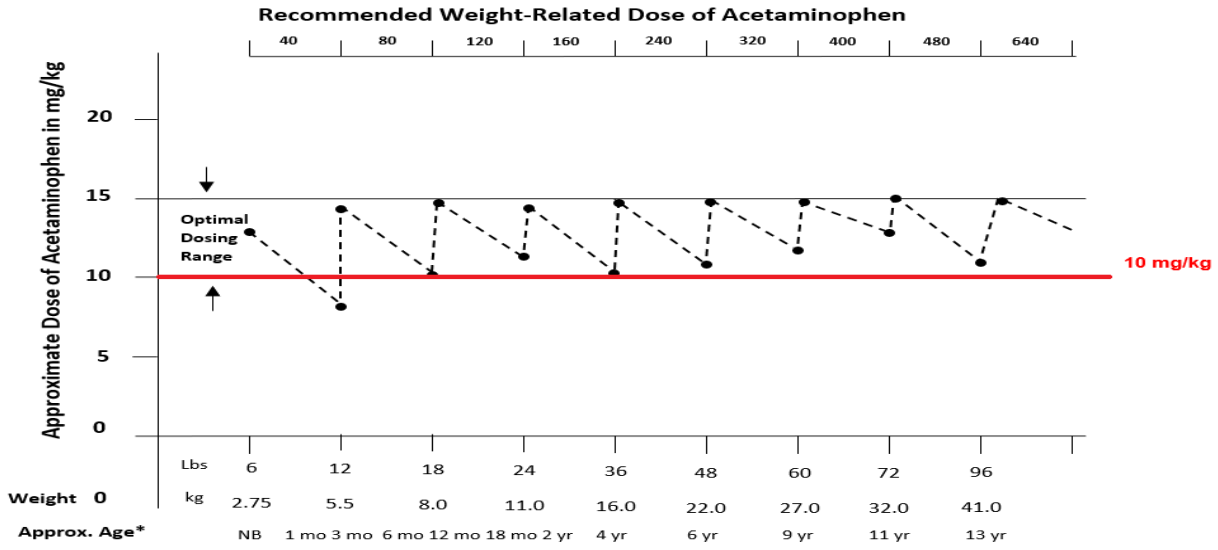
As highlighted herein, Dr. Temple's weight-based schedule was developed to narrowly define age ranges and importantly, specified weight ranges to keep a more consistent mg/kg dosing pattern to an optimized therapeutic dosing range. It is specifically the purpose of this petition and its proposed dosing amendments, to enhance this mg/kg dosing range to an exact dose to individual patient weight, solely as a predetermined (mg) dose to specific weight (kg) dose.

In fact the FDA's Briefing Information for the June 29-30, 2009 Joint Meeting of the Drug Safety and Risk Management Advisory Committee with the Anesthetic and Life Support Drugs Advisory Committee and the Nonprescription Drugs Advisory Committee [17] proposes as a first option to, "Reduce current doses (e.g., current maximum adult daily dose, single adult dose, and tablet strength) as acetaminophen has a narrow safety margin. This means there is little difference between the maximum daily dose and a potentially harmful dose. This option involves reducing the amount of acetaminophen recommended as a daily dose for OTC, and perhaps also Rx products, to decrease the likelihood that patients will unintentionally exceed safe doses"[17]

Background Support for Additional Dose-to-Weight Dosing Method to TFM

As established, decades of large-scale trials have concluded that a minimum dose of 10 mg/kg is safe and efficacious, therefore a consistent 10 mg/kg dose (Figure 8), within the "optimal dosing range" of 10-15 mg/kg, would provide a consistent efficacious dose to a specific individual patient weight. Moreover, in parallel this dosing would provide an enhanced margin before reaching the upper dose limit and perhaps administering a supratherapeutic dose, in contrast to the current weight-based dosing schedule, (Figure 6).

Figure 8. Temple Weight Based Dosage Schedule - Example with 10 mg/kg Dose



Temple, A.R., "Pediatric dosing of acetaminophen" Pediatric Pharmacology 1983: 3:321-327

The proposed amendments herein enhances dose consistency of the medication, which seems to be as originally intended by Temple's 1983 novel pediatric weight based dosing schedule developed in large part to; "provide gradual dosing increments as the child increases in weight" and as well, "to avoid the inherent mg/kg variability from age-based dosing."[10]

Dose-to-Weight Compliance within Published TFM

Table 1. Published 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**

The existing TFM provides for a set dose of 160 or 162 mg for all children within a range of 2 years of age to under 4 years of age, (Table 1), without any other dosing option. Additional dosing methods for a dose to individual weight, would provide for a narrowed consistent dose throughout the 2-4 years of age range of either 10.00 mg/kg or 10.14 mg/kg to a child's individualized weight. Moreover, the additional dose to patient weight dosing schedule would also harmonize with the published TFM, as well as the commercially available single-ingredient acetaminophen oral suspensions of 160 mg per 5mL, (Figure 9).

Figure 9. Proposed Dose-to-Weight Dosage Schedules

Dose-to-Weight Example Acetaminophen 161mg/5mL		
lb.	mg	mg/lb
6	27.6	4.6
7	32.2	4.6
8	36.8	4.6
9	41.4	4.6
10	46.0	4.6
11	50.6	4.6
12	55.2	4.6
13	59.8	4.6
14	64.4	4.6
15	69.0	4.6
16	73.6	4.6
17	78.2	4.6
18	82.8	4.6
19	87.4	4.6
20	92.0	4.6
21	96.6	4.6
22	101.2	4.6
23	105.8	4.6
24	110.4	4.6
25	115.0	4.6
26	119.6	4.6
27	124.2	4.6
28	128.8	4.6
29	133.4	4.6
30	138.0	4.6
31	142.6	4.6
32	147.2	4.6
33	151.8	4.6
34	156.4	4.6
35	161.0	4.6
Dose (10.14 mg/kg)		4.60mg/lb.

Dose-to-Weight Example Acetaminophen 160mg/5mL		
lb.	mg	mg/lb
6	27.4	4.57
7	32.0	4.57
8	36.6	4.57
9	41.1	4.57
10	45.7	4.57
11	50.3	4.57
12	54.8	4.57
13	59.4	4.57
14	64.0	4.57
15	68.6	4.57
16	73.1	4.57
17	77.7	4.57
18	82.3	4.57
19	86.8	4.57
20	91.4	4.57
21	96.0	4.57
22	100.5	4.57
23	105.1	4.57
24	109.7	4.57
25	114.3	4.57
26	118.8	4.57
27	123.4	4.57
28	128.0	4.57
29	132.5	4.57
30	137.1	4.57
31	141.7	4.57
32	146.2	4.57
33	150.8	4.57
34	155.4	4.57
35	160.0	4.57
Dose (10.00 mg/kg)		4.57mg/lb.

Figure 10. Proposed Amendment to TFM, with Additional 10mg-to-kg Patient Weight

Weight (Lb.)	mg	Age
24	109.7	2 – 3 Years
25	114.3	
26	118.8	
27	123.4	
28	128.0	
29	132.5	
30	137.1	
31	141.7	
32	146.2	
33	150.8	
34	155.4	
35	160.0	

B) Dosage Unit Amendments

Figure 1. Published 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

The dosage units indicated within the TFM (Figure 1), provided for apportioning a solid children's single-ingredient acetaminophen dosage unit. The TFM is absent any other dosage units and/or directions for any oral suspension dosage units, although the most popular dosage unit for the children's age group of 2-4 years of age. A supplemental correlating volumetric measurement to the existing dosage schedule of 160–162 mg for the patient range of 2-4 years of age, would provide dosing for oral suspensions, as well provide for another correlating indicia for reverification of the intended dose. The addition of an oral suspension dosage unit and volumetric dosing units thereof, would also harmonize current commercial dosing practices and the published TFM, (Figure 11).

Expanded Volumetric Dosing Compliance Within TFM

Additional and expanded volumetric (mL) dosing directions continue to comply with the TFM, Children's Dosage Schedule for Acetaminophen of 160mg, (Figure 11).

Figure 11. Proposed Volumetric Dosage Schedule

Enhanced Volumetric Dosage Example		
Acetaminophen 160mg/5mL		
Lb	mL	mg/lb
24	3.43	4.57
25	3.57	4.57
26	3.71	4.57
27	3.86	4.57
28	4.00	4.57
29	4.14	4.57
30	4.28	4.57
31	4.43	4.57
32	4.57	4.57
33	4.71	4.57
34	4.86	4.57
35	5.00	4.57
Average (10mg/kg)		4.57mg/lb.

Figure 12. Proposed Amendment to TFM with volumetric dosing correlated to patient weight or age.

Weight (Lb.)	mg	Age	mL
24	109.7	2 – 3 Years	5 mL
25	114.3		
26	118.8		
27	123.4		
28	128.0		
29	132.5		
30	137.1		
31	141.7		
32	146.2		
33	150.8		
34	155.4		
35	160.0		

C) Enhanced Drug Concentration Indicia

Figure 1. Published, TFM Monograph, 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

Enhanced Drug Concentration Indicia Compliance Within Current TFM

The existing TFM (Figure 1), provides for a set dose of 160 or 162 mg for children within a range of 2 to under 4 years of age. The TFM is absent any alternative mode for tapering or enhanced this dosage to any individual patient specificity within the published TFM. Thus, the absence of a published optimal set dose in potency and/or volume, eliminates any mechanism for dosing delivery enhancement especially for oral suspensions.

Figure 13. Example of Enhanced Potency or Volume Dosage Schedule

Enhance Drug Dosage Example		
Acetaminophen 160mg/5mL		
lb	mL	mg/lb
6	0.86	4.57
7	1.00	4.57
8	1.14	4.57
9	1.29	4.57
10	1.43	4.57
11	1.57	4.57
12	1.71	4.57
13	1.86	4.57
14	2.00	4.57
15	2.14	4.57
16	2.29	4.57
17	2.43	4.57
18	2.57	4.57
19	2.71	4.57
20	2.86	4.57
21	3.00	4.57
22	3.14	4.57
23	3.28	4.57
24	3.43	4.57
25	3.57	4.57
26	3.71	4.57
27	3.86	4.57
28	4.00	4.57
29	4.14	4.57
30	4.28	4.57
31	4.43	4.57
32	4.57	4.57
33	4.71	4.57
34	4.86	4.57
35	5.00	4.57
Average (10mg/kg)		4.57mg/lb.

Enhance Drug Dosage Example		
Acetaminophen 160mg/5mL		
Lb	mg	mg/lb
6	27.4	4.57
7	32.0	4.57
8	36.6	4.57
9	41.1	4.57
10	45.7	4.57
11	50.3	4.57
12	54.8	4.57
13	59.4	4.57
14	64.0	4.57
15	68.6	4.57
16	73.1	4.57
17	77.7	4.57
18	82.3	4.57
19	86.8	4.57
20	91.4	4.57
21	96.0	4.57
22	100.5	4.57
23	105.1	4.57
24	109.7	4.57
25	114.3	4.57
26	118.8	4.57
27	123.4	4.57
28	128.0	4.57
29	132.5	4.57
30	137.1	4.57
31	141.7	4.57
32	146.2	4.57
33	150.8	4.57
34	155.4	4.57
35	160.0	4.57
Average (10mg/kg)		4.57mg/lb.

An amended TFM further denoting the volume and/or potency of the 160 or 162 mg/5mL children's acetaminophen that is subsequently correlated to an individual child's physical characteristic(s), would provide a caregiver an optional dosing method to dose a child at a higher degree of specificity within the patient range, (Table 14).

Figure 14. Options to TFM with additional (mg) potency or volume (mL) dosing, Figure 14(a) & 14(b)

Figure 14(a)

Weight (Lb.)	mg	Age	mL
24	109.7	2 – 3 Years	5 mL
25	114.3		
26	118.8		
27	123.4		
28	128.0		
29	132.5		
30	137.1		
31	141.7		
32	146.2		
33	150.8		
34	155.4		
35	160.0		

Figure 14(b)

Weight (Lb.)	mL	Age	mg
24	3.43	2 – 3 Years	160 mg
25	3.57		
26	3.71		
27	3.86		
28	4.00		
29	4.14		
30	4.28		
31	4.43		
32	4.57		
33	4.71		
34	4.86		
35	5.00		

5. Domestically Marketed product under existing TFM

Dozens of studies have concluded one of the leading dosing errors occur due to the difficulty of understanding the directions on the medication label.[14,18,19,20,21]

The directions of commercially marketed products deemed in compliance with the TFM, are enhanced by the proposed TFM amendments as described herein as, A, B, C.

Figure 15. Commercially Available Product

Figure 16. Commercially Available Product (6C)

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

6A) Directions correctly provide pursuant to FDA Panel Recomendations[1]; "if possible, use weight to dose if otherwise, use age." Conversely, there is no dose to weight option to choose from, only a set dose of 160 mg/5mL for the configured product for a 24-35 lb. child range.

6B) The product provides for a dose of 160 mg absent any option for further tapering or enhancing the dose in any way to either patient characteristic (weight or age), deemed relevant to express as a "dosing" direction.

6C) The product provides for a 5 mL set dose absent any option for further tapering or enhancing the dose in any way to either patient characteristic (weight or age), deemed relevant to express as a "dosing" direction.

6. Requested Amendments to the Existing TFM

The petitioner hereby requests that the United States Food and Drug Administration make the requested amendments to the published dosage schedule for use of over-the counter children's single-ingredient acetaminophen for 2-4 years of age as published on November 16, 1998, in the United States Tentative Final Monograph for Internal Analgesic, Antipyretic and Antirheumatic Drug Products, as herein indicated below, (Figure 17a,b).

Figure 17(a) Requested Final Amendment (Option 1)

Weight (Lb.)	mg	Age	mL
Under 24	Ask a Doctor	Under 2 years	Ask a Doctor
24	109.7	2 – 3 Years	5 mL
25	114.3		
26	118.8		
27	123.4		
28	128.0		
29	132.5		
30	137.1		
31	141.7		
32	146.2		
33	150.8		
34	155.4		
35	160.0		

Figure 17(b) Requested Final Amendment (Option 2)

Weight (Lb.)	mL	Age	mL
Under 24	Ask a Doctor	Under 2 years	Ask a Doctor
24	3.43	2 – 3 Years	5 mL
25	3.57		
26	3.71		
27	3.86		
28	4.00		
29	4.14		
30	4.28		
31	4.43		
32	4.57		
33	4.71		
34	4.86		
35	5.0		

In the case of either of the above requested amendments being implemented, the proposed amendment would provide for the available dosing method currently absent within the commercially labeled product and directions as illustrated below.

Directions

- this product does not contain directions or complete warnings for adult use
- do not give more than directed (see overdose warning)
- shake well before using
- mL = milliliter
- find right dose on chart. If possible, use weight to dose on chart otherwise use age
- push air out of syringe. Insert syringe tip into bottle opening
- flip bottle upside down. Pull plunger of syringe to correct dose
- dispense liquid slowly into child's mouth, toward inner cheek
- repeat dose every 4 hours while symptoms last
- do not give more than 5 times in 24 hours
- replace cap tightly to maintain child resistance

7. Conclusion

The petitioner respectfully requests the FDA to take immediate action to ensure millions of children have an opportunity to receive over-the-counter single-ingredient acetaminophen to the highest standard of care and dosing accuracy as now commercially available and described herein. The FDA should publish a statement of enforcement, permitting these additional dosing methods and directions, thus affording dosing accessibility for enhancing dose precision through one or more known physical characteristics of a child.

The proposed amendments to the TFM as herein presented, provide simplistic labeling changes that continue to provide a dosing schedule in compliance within the established TFM dosage schedule. In parallel, the additional dosing methods correlate a specific set dose to one or more patient characteristic, thus also allowing for visual reverification of the intended dose. More importantly, these proposed amendments also provide for an enhanced narrowed dosing schedule for those caregivers, knowing the child's individual specific weight, while continuing to provide all existing dosing features unchanged within the existing TFM.

The petitioner unequivocally agrees with the FDA Panel that maintaining a weight and age dosing indicia is highly effective in the dosing administration in children. This configuration provides important reverification of the intended dose, should both weight and age be known, or at least one method should only one child characteristic be known. Conversely, the petitioner vehemently disagrees with any assertion that the majority of caregivers dispensing medication to a child of 2-4 years of age (during the age of multiple pediatricians visits), would not already know or could not ascertain the child's exact weight and/or or exact month of age.

As such, this non-clinical assumption could adversely affect millions of children from receiving, what very well may be a safer dose of single-ingredient acetaminophen.

Notwithstanding, there are no proposed amendments within this petition that would prevent the current dosage schedule under the existing TFM from being utilized. In fact, only the caregivers that desire to further enhance a dose of medication through one or more dosing methods (to be as precise as possible), are penalized along with the intended child by the lack of specificity within the published TFM dosage schedule.

8. 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).

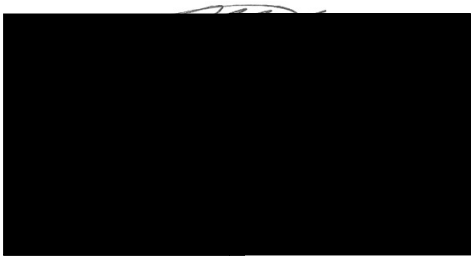
9. Economic Impact

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

10. 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,



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