McNeil Consumer Healthcare, 7050 Camp Hill Road, Fort Washington, PA 19034-2299 (215) 273-7000

Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fisher Lane (Room 1061)
Rockville, MD 20852

AUG 15 2001

01 AUG 16 A9:57

RE: Docket No. 77N-0094
Comment No. CP14
Amendment to Citizen Petition dated 2/1/99
Expanded Age Groups for OTC Consumer Dosing Instructions
Covering Acetaminophen

Dear Sir/Madame:

We are submitting this letter and data in follow-up to a written request (attached) that was discussed with HFD-560 and OPDRA on 9/22/00 via teleconference. McNeil was requested to provide the data source that was used for the age and weight ranges contained in the chart for dosing acetaminophen in children less than 2 years of age that was included in our Citizen Petition dated 2/1/99. Our petition requested that the directions for use covering pediatric acetaminophen products in the **TFM** for Internal Analgesics be amended to expand the age groups for OTC consumer dosing instructions. The agency noted that the weights for children less than 2 years of age, on McNeil's dosing chart, do not represent average weights for US children in this age category. In the 9/22/00 teleconference, agency representatives suggested that the petition's proposed weight ranges are too low for the accompanying age ranges and suggested that this could lead to potential dosing errors. McNeil agreed to evaluate this issue and formulate a proposal for discussion and review by HFD-560 and OPDRA.

Data Sources for the Age and Weight Ranges

As mentioned in our original petition, in 1983 McNeil, on its own initiative, developed an age-based and a weight-based dosing schedule for health care professionals based on dosing schedules first proposed in a publication that year [Temple, 1983]. These schedules have been widely used and are currently found on OTC acetaminophen products. Similar schedules using the same age-breaks and weight-breaks are found on OTC ibuprofen products.

Weight-based dosing schedule:

When originally published [Temple 1983], the weight-based dosing schedule was based empirically on weight ranges that would allow for incremental increases in dose consistent with incremental increases in weight. Consequently, the dose of acetaminophen would be within the effective and safe range of 10-15 mg/kg/dose.

77N-0094

SUP 45

The dosing schedules were based on incremental increases of 40 or 80mg, consistent with the 80mg dosing unit then available for acetaminophen (concentrated drops: 40mg/0.4ml or 80mg/0.8ml; liquids: 80mg/1/2tsp (2.5ml); chewable tablets: 80mg/tablet). Thus, the weight-based schedule shown in Table 1 was recommended.

Table 1. Weight-based schedule for the pediatric dosing of acetaminophen – Original Schedule. (Adapted from Temple, 1983)

Table 1. Weight-Based Schedule For The Pediatric Dosing Of Acetaminophen
Original Schedule. (Adapted from Temple, 1983)

Weight (lbs)	Weight (kgs)	Acetaminophen Dose (mg)	Dosing Range (mg/kg)
6-11	2.5-5.4	40	7.4-16.0
12-17	5.5-7.9	80	10.1-14.5
18-23	8.9-10.9	120	11.0-15.0
24-35	11.0-15.9	160	10.0-14.5
36-47	16.0-21.9	240	10.9-15.0
48-59	22.0-26.9	320	11.9-14.5
60-71	27.0–31.9	400	12.5-14.8
72-95	32.0-43.9	480	10.9-15.0
96 +	44.0 +	640	-14.5

Note that this schedule was developed independent of any specific set of weights for given ages. As a result, it remains a constant and consistent way to dose acetaminophen in the range of 10-15mg/kg/dose. There is no need to alter this schedule.

Age-based dosing schedule:
Aware that a parent or caregiver might not know a child's weight, in addition to a weight-based schedule, McNeil continues to use an age-based schedule. In the original publication in 1983, the data for determining doses in mg/kg that would be administered for each of the age ranges was developed using the National Center for Health Statistics (NCHS) reported data from the National Health and Nutrition Examination Survey (NHANES II Survey). This age-based schedule used increments of age that would allow for incremental increases in dose consistent with an average child's growth over these age ranges. The actual dosing range was verified by using NHANES II 10th to 90th percentile weights for age, averaged for boys and girls. Each dosing range is based on the smallest child for the age range (youngest month, 10th percentile weight) and the largest child for the age range (oldest month, 90th percentile weight). Table 2 summarizes the recommended dose for each of the age ranges and an estimated dosing range that would result from the use of that dose.

Table 2. Age-based schedule for the pediatric dosing of acetaminophen - Original schedule. (Adapted from Temple, 1983)

Table 2. Age-Based Schedule For The Pediatric Dosing Of Acetaminophen Original Schedule. (Adapted from Temple, 1983)		
Age (mos/yrs)	Acetaminophen Dose (mg)	Dosing Range (mg/kg)
Under 4mos	40	5.9-14.9
4-11mos	80	7.0-14.7
12-23mos	120	8.0-14.8
2-3yrs	160	7.5-14.0
4-5yrs	240	9.5-16.5
6-8yrs	320	9.5-17.0
9-10yrs	400	9.0-16.5
11yrs	480	9.8-16.2
12yrs +	640	8.0-17.0

Distinction Between the Two Dosing Schedules:
The weight-based schedule was questioned based on what appears to be the assumption that the weight-based schedule in the proposed dosing chart is tied to the average weights in the age-based schedule. However, as stated above, the weights presented in the weight-based schedule in the proposed dosing chart are not tied to the average weights for children of the ages presented in the age-based schedule. The two schedules (age-based, weight-based) were constructed using two separate approaches to provide for incremental dosing. They are related only in principle. They both provide for incremental increases in dosing as the child grows; and they both attempt to provide for acetaminophen dosing that approximates 10-15 mg/kg/dose.

An example using the age-based schedule dose for a 2-3 year old of 160mg is illustrative. When the weight-based schedule was established, the weight range assigned to the 160mg dose was done empirically, and resulted in the selection of an 11-15.9kg or 24-35lb range. This range was selected to give the correct mg/kg dose, not to coincide with average weights for 2-3 year olds. In fact, the range of weights for 2-3 yr olds is 10.3-18.5kg (22-41lb) if you use data for the very small-for-age 10th percentile 2 year old and the very large-for-age 90th percentile 3 year 11 month old.

As a result, when a dose in mg/kg is calculated using these two dosing schedules, the results are somewhat different. For a 2-3yr old given a 160mg dose (the age-based schedule), the dose ranges from 8.6-16.2mg/kg/dose. When a child in the 24-35 lb range is given a 160mg dose (age-based schedule), a narrower range of 10.0-14.5mg/kg/dose is obtained. Thus, in considering new weight-for-age data, any changes to the standard dosing schedules currently being used would apply only to the age-based schedule.

Average Weights for U.S. Children by Age: Impact on Age-based Schedule

The agency has stated that they have reviewed the current growth charts for U.S. children, published by the Center for Disease Control and Prevention/National Center for Health Statistics (CDC/NCHS). Based on these new data, the agency has suggested that the weights for children less than 2 years of age, using the dosing chart submitted with the original McNeil Consumer Healthcare petition, no longer represent average weights for U.S. children in these age categories, so that adjustments may need to be made in the age-based schedule.

NHANES III Weight-For-Age Data: Impact On Current Age-Based Schedule

We obtained the data from tables provided by the Centers for Disease Control at their web site: http://www.cdc.gov/nchs/about/major/nhanes/growthcharts/datafiles.htm. For our analysis, we were able to obtain the data tables of weight-for-age percentiles for boys and girls, birth to 36 months and 2 to 20 years. The weights for a given age and percentile for boys and girls were averaged. The following table summarizes the data used for this analysis.

Table 3. Selected average weights by age for various body-weight percentiles from the NHANES III Study, listed by gender, with author-calculated averages (weights in kg).

	Boys			Girls			Average		
Age (mo)	10th	50th	90th	19th	50th	90th	10th	50th	90th
1.5	4	4.9	5.7	3.8	4.5	5.3	3.9	4.7	5.5
3.5	5.4	6.4	7.5	5	5.9	6.8	5.2	6.2	7.2
4.5	6	7	8.2	5.5	6.4	7.5	5.8	6.7	7.8
6.5	7	8.2	9.5	6.4	7.5	8.6	6.7	7.8	9
9.5	8.2	9.5	11	7.5	8.7	10	7.8	9.1	10.5
10.5	8.5	9.8	11.4	7.9	9	10.4	8.2	9.4	10.9
11.5	8.8	10.2	11.7	8.2	9.4	10.8	8.5	9.8	11.2
12.5	9.1	10.5	12.1	8.4	9.7	11.1	8.8	10.1	11.6
17.5	10.1	11.6	13.4	9.6	10.9	12.5	9.8	11.2	13
23.5	11	12.7	14.5	10.5	11.9	13.8	10.8	11.4	14.2
24.5	11.1	12.7	14.7	10.6	12.1	14	10.9	12.4	14.4
35.5	12.4	14.3	16.5	12	13.8	16.3	12.2	14	16.4

Table 4 shows the dosing ranges that result when the doses currently being used for a given age are calculated against these new weights for age.

Table 4. NHANES III Weights for Age: Standard Acetaminophen Dosing

Age in Months	Weight in Kg by Percentile 10th	50th	90th	Dose (mg)	Dose in mg/kg Mean	Range
1.5	3.9	4.7	5.5	40	8.5	7.3-10.3
2.5	4.6	5.4	6.4	40	7.4	6.2-8.7
3.5	5.2	6.2	7.2	40	6.4	5.6-7.7
4.5	5.8	6.7	7.8	80	11.9	10.3-13.8
6.5	6.7	7.8	9.0	80	10.3	8.9-11.9
9.5	7.8	9.1	10.5	80	8.8	7.6-10.3
10.5	8.2	9.4	10.9	80	8.5	7.3-9.8
11.5	8.5	9.8	11.2	80	8.2	7.1-9.4
12.5	8.8	10.1	11.6	120	11.9	10.3-13.6
17.5	9.8	11.2	13.0	120	10.7	9.2-12.2
23.5	10.8	11.4	14.2	120	10.5	8.4-11.1
24.5	10.9	12.4	14.4	160	12.9	11.1-14.7
35.5	12.2	14.0	16.4	160	11.4	9.8-13.1

If these same weights are used to recalculate the dosing ranges for the age-based schedule using the original schedule's age ranges and the new age-weight norms, the results show a modified set of ranges (Table 4). The dosing ranges in Table 5 are based on the smallest child for the age range (youngest month, 10th percentile weight) and the largest child for the age range (oldest month, 90th percentile weight). These data represent dosing ranges for the original age-based schedule.

Table 5. Age-based schedule for the pediatric dosing of acetaminophen – Original age-ranges, using new age-weight norms.

Age	Acetaminophen	
Months	Dose (mg)	Dosing Range (mg/kg)
Under 4	40	5.6-10.3
4-11	80	7.1-13.8
12-23	120	8.4-13.6
Years		
2-3	160	9.8-14.7

Alternate Age-based Schedules Using NHANES III Weight-For-Age Data:
This same approach can be used to assess alternative age-based schedules for the pediatric dosing of acetaminophen, using modified age ranges and the new data age-weight norms. Table 6 evaluates one such alternative. It shows dosing ranges when the dose for children ages 3.5 mos is increased to 80mg (from 40mg) and the dose for 11.5 mos is increased to 120mg (from 80 mg).

Table 6. NHANES III Weights for Age: Modified Acetaminophen Dosing.

Age in Months	Weight in Kg by Percentile			Dose		
	10th	50th	90th	(mg)	Mean	Range (mg/kg)
1.5	3.9	4.7	5.5	40	8.5	7.3-10.3
2.5	4.6	5.4	6.4	40	7.4	6.2-8.7
3.5	5.2	6.2	7.2	80	12.9	11.1-15.4
4.5	5.8	6.7	7.8	80	11.9	10.3-13.8
6.5	6.7	7.8	9.0	80	10.3	8.9-11.9
9.5	7.8	9.1	10.5	80	8.8	7.6-10.3
10.5	8.2	9.4	10.9	80	8.5	7.3-9.8
11.5	8.5	9.8	11.2	120	12.2	10.7-14.1
12.5	8.8	10.1	11.6	120	11.9	10.3-13.6
17.5	9.8	11.2	13.0	120	10.7	9.2-12.2
23.5	10.8	11.4	14.2	120	10.5	8.4-11.1
24.5	10.9	12.4	14.4	160	12.9	11.1-14.7
35.5	12.2	14	16.4	160	11.4	9.8-13.1

Table 7 presents a recommended schedule, which involves changing the age ranges to the following intervals: birth to 5 months; 6 to 10 months; and 11-23 months, with no modifications made for children ages 2 years (24 months) and older. Dosing ranges are based on the smallest child for the age range (youngest month, 10th percentile weight) and the largest child for the age range (oldest month, 90th percentile weight).

Table 7. Age-based schedule for the pediatric dosing of acetaminophen. Modified schedule, using modified age-ranges and new age-weight norms.

Age	Acetaminophen	
Months	Dose (mg)	Dosing Range (mg/kg)
Under 6	Use weight-based dosing schedule	
6-10	80	7.3-12.3
11-23	120	8.4-14.3
Years		
2-3	160	9.8-14.7

The only changes in this age-based schedule involve children 11 months of age. For the 90th percentile 11-month-old, the new schedule would provide a dose of 10.7mg/kg versus a dose of 7.1mg/kg with the older schedule. For the 10th percentile 11-month-old, the new schedule would provide a dose of 14.1mg/kg versus a dose of 9.4mg/kg with the older schedule.

Summary

Thus, our recommendation for the dosing schedule for acetaminophen containing products for children under 2 years of age is to adopt the schedule proposed in Table 7 with the following specific recommendations:

- Provide the weight-based schedule for the full range of pediatric weights, for weight of 12 lbs and higher, with a statement to the effect that when dosing children, dosing by weight is preferred, and that only if weight is not known should the age-based schedule be used.

- Provide the age-based schedule for children age 6 months and older. For children under age 2 years use the following age ranges and doses: birth to 5 months - see weight schedule; 6 to 10 months – 80mg; and 11-23 months – 120mg. Age ranges and doses for children ages 2 years and older would remain the same as currently used.

Since acetaminophen would only have a dose on the label for children 6 months of age and older, we would strongly urge that McNeil and other manufacturers be allowed to give healthcare professionals the appropriate recommended dosing information for children under 6 months of age and under 12 lbs body weight based on the dosing schedule of 10-15mg/kg/dose up to 5 doses per day.

We trust that this information responds appropriately to the agency's inquiry regarding the dosing schedule for children under 2 years of age. For further information or discussion, please contact either Anthony R. Temple, MD, at 215-273-7763 or me at 215-273-7878.

Sincerely,

McNEIL CONSUMER HEALTHCARE

Paula J. Oliver

Paula J. Oliver
Senior Director
Regulatory Affairs

cc (Letter only): C. Ganley, MD (HFD-560)
L. Katz, MD (HFD-560)
W. Ellenberg, Ph.D. (HFD-560)

Attachments

P:\PJO0652

Food and Drug Administration
Rockville MD 20857

Paula J. Oliver
Senior Director, Regulatory Compliance
McNeil Consumer Healthcare
7050 Camp Hill Road
Fort. Washington, Pennsylvania 19034

APR 18 2001

Re: Docket No. 77N-0094
Comment No. CP14

Dear Ms. Oliver:

This letter is sent in reference to your citizen petition dated February 1, 1999. The petition is filed as CP14 in Docket No. 77N-0094 in FDA's Dockets Management Branch. The petition requests that the agency amend the Tentative Final Monograph for Over-the-Counter Internal Analgesic, Antipyretic, and Antirheumatic Drug Products (53 FR 46204, November 16, 1988) to expand the proposed dosing directions for children to include children under 2 years of age. Specifically, the petition seeks expansion of the proposed dosing directions to include: (1) Dosing down to 2 months of age for concentrated infant acetaminophen products (80 mg/ 0.8 mL); (2) dosing down to 4 months of age for less concentrated acetaminophen products (160 mg/teaspoon); (3) weight and age based dosing for these products; and (4) a statement in the directions of concentrated products that states: Always call doctor for fever in children under age 4 months. Your petition further requests that FDA promptly publish an enforcement policy in the FEDERAL REGISTER to permit the marketing of OTC acetaminophen drug products bearing expanded pediatric labeling pending establishment in the final monograph.

In a telephone conversation with representatives of your company dated September 22, 2000, the agency noted that the petition's proposed weight ranges are too low for the accompanying age ranges, and raised the concern that this could lead to dosing errors. In response to this concern, McNeil representatives agreed to look into the issue and formulate a proposal for discussion. To date, we have not received your proposal. We would like to complete our evaluation of your petition and request that you provide your proposal or a response to our request within the next 30 days.

Your proposal should be submitted as an amendment to your petition to the Dockets Management Branch (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. All correspondence regarding this matter should reference the docket and comment number noted above and be submitted to the Dockets Management Branch.

Sincerely yours,

Charles J. Ganley, M.D.
Director
Division of OTC Drug Products

FedEx Express USA Airbill

FedEx Tracking Number 8287 4198 7136

Form I.D. No. 0215 — Recipient's Copy

RECIPIENT: PEEL HERE

1 From This portion can be removed for Recipient's records.

Date 8/15/2001 FedEx Tracking Number 828741987136

Sender's Name MAUREEN BARRON Phone 215 273-7000

Company MCNEIL CONSUMER HEALTHCARE

Address 7050 CAMP HILL RD Dept/Floor/Suite/Room

City FORT WASHINGTON State PA ZIP 19034

2 Your Internal Billing Reference 01628117470000000

3 To

Recipient's Name Dockets Management Branch Phone

Company Food and Drug Administration

Address 5630 Fisher Lane (Room 1061)

To "HOLD" at FedEx location, print FedEx address. We cannot deliver to P.O. boxes or P.O. ZIP codes.

Dept./Floor/Suite/Room

City Rockville State MD ZIP 20852

8287 4198 7136

0181783109

4a Express Package Service — *Packages up to 150 lbs.* Delivery commitment may be later in some areas.

- [x] FedEx Priority Overnight* Next business morning.
- [ ] FedEx Standard Overnight Next business afternoon
- [ ] FedEx First Overnight Earliest next business morning delivery to select locations
- [ ] FedEx 2Day Second business day
- [ ] FedEx Express Saver Third business day
- [ ] **NEW** FedEx Extra Hours Later drop-off with next business afternoon delivery for select locations

FedEx Envelope rate not available. Minimum charge: One-pound rate

4b Express Freight Service — *Packages over 150 lbs.* Delivery commitment may be later in some areas.

- [ ] FedEx 1Day Freight* Next business day
- [ ] FedEx 2Day Freight Second business day
- [ ] FedEx 3Day Freight Third business day

* Call for Confirmation:

5 Packaging * Declared value limit $500

- [x] FedEx Envelope*
- [ ] FedEx Pak* Includes FedEx Small Pak, FedEx Large Pak, and FedEx Sturdy Pak
- [ ] Other Pkg. Includes FedEx Box, FedEx Tube, and customer pkg.

6 Special Handling Include FedEx address in Section 3.

- [ ] **SATURDAY Delivery** Available only for FedEx Priority Overnight and FedEx 2Day to select ZIP codes
- [ ] **SUNDAY Delivery** Available only for FedEx Priority Overnight to select ZIP codes
- [ ] **HOLD Weekday** at FedEx Location Not available with FedEx First Overnight
- [ ] **HOLD Saturday** at FedEx Location Available only for FedEx Priority Overnight and FedEx 2Day to select locations

Does this shipment contain dangerous goods? One box must be checked.

- [x] No
- [ ] Yes As per attached Shipper's Declaration
- [ ] Dry Ice Dry Ice, 9, UN 1845 ____ x ____ kg
- [ ] Cargo Aircraft Only

Dangerous Goods (incl. Dry Ice) cannot be shipped in FedEx packaging or with FedEx Extra Hours service.

7 Payment *Bill to:* Enter FedEx Acct. No. or Credit Card No. below.

- [x] Sender Acct. No. in Section 1 will be billed.
- [ ] Recipient
- [ ] Third Party
- [ ] Credit Card
- [ ] Cash/Check
- [ ] Obtain Recip. Acct. No.

Total Packages	Total Weight	Total Charges
		Credit Card Auth.

†Our liability is limited to $100 unless you declare a higher value. See the *FedEx Service Guide* for details.

8 Release Signature *Sign to authorize delivery without obtaining signature.*

By signing you authorize us to deliver this shipment without obtaining a signature and agree to indemnify and hold us harmless from any resulting claims.

Questions? Visit our Web site at fedex.com or call 1-800-Go-FedEx® (800)463-3339.

SRS•Rev. Date 12/00•Part #155818S•©1994–2000 FedEx•PRINTED IN U.S.A.

406