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Dockets Management Branch  
U. S. Food and Drug Administration  
Central Document Room  
5630 Fishers Lane Rm. 1061  
Rockville, MD. 20852

Re: Docket No. 1982N-0166  
Orally Administered Drug Products for Relief of Symptoms  
Associated with Overindulgence in Food and Drink for Over-the-  
Counter Human Use; Tentative Final Monograph [21CFR357  
Subpart J], 56 Federal Register 247

To Whom It May Concern:

The Procter & Gamble Company (Procter & Gamble) per a telephone request from Ms. Laura Shay, FDA ODE V, Division of OTC Drugs, herewith submits, in triplicate, 4 studies and additional literature documents requested by the FDA and makes further recommendations in support of our original submission to the FDA, dated April 21, 1991, pursuant to the Tentative Final Monograph for Orally Administered Drug Products for Relief of Symptoms Associated with Overindulgence in Food and Drink for Over-the-Counter Human Use, published in the Federal Register December 24, 1991.

The data in this submission support the following recommendations:

1. **Indications (proposed 21CFR357.950(b)) – Indigestion Indication**

**Procter & Gamble continues to recommend that ‘indigestion’ be added to the symptoms associated with upset stomach due to overindulgence and drink. We continue to recommend that the specific indication be “for the relief of upset stomach associated with” (select one or more of the following: “indigestion”, “nausea”, “heartburn”, and “fullness”) “due to overindulgence in food and drink”.**

Consumers consider ‘upset stomach’ and ‘indigestion’ as synonymous terms, as consumers commonly use the term ‘indigestion’ to describe symptoms of upset stomach due to overindulgence in food and drink. Adding the term ‘indigestion’ would also make the upset stomach symptoms due to overindulgence in food and drink more consistent between antacid and ‘upset stomach relievers’.

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The similarity between the terms ‘indigestion’ and ‘upset stomach’ was confirmed in a consumer research study (Study PD # 0390-54, The Procter & Gamble Co., see report in Appendix 1) conducted to determine the consumer definition of indigestion relative to other stomach discomfort symptoms. In this study a US nationally representative sample of 1,158 adults (18 years or older) completed a mail-back, self-administered questionnaire. Consumers were asked what they used to describe the feeling of: a) indigestion, b) upset stomach, c) heartburn, d) nausea, and e) fullness/bloating. The words used to describe feelings associated with ‘indigestion’ and ‘upset stomach’, with respect to the symptoms for which bismuth subsalicylate has Category I status, were virtually indistinguishable.

The consumer perception that ‘indigestion’, ‘acid indigestion’, and ‘upset stomach’ are synonymous terms is supported by another consumer study (Study PD # 1083-53, The Procter & Gamble Co., see report in Appendix 2), which was conducted to develop a comprehensive consumer-based understanding of common gastrointestinal symptoms. In this study a US nationally representative sample of 310 adults (18 years and older) completed a mail-back, self-administered questionnaire. Results showed the terms ‘upset stomach’, ‘indigestion’ and ‘acid indigestion’ are terms used by consumers to describe the same symptom.

**2. Directions (proposed 21CFR357.959(d)) – Children’s Doses**

**The tentative final monograph does not include directions for the use of bismuth subsalicylate by children under 12 years of age. We continue to recommend that the monograph be amended to include dosage regimens for bismuth subsalicylate for relief of upset stomach due to overindulgence in food and drink in children aged 3 – 12 years. We also recommend that the adult dose for bismuth subsalicylate for relief of upset stomach due to overindulgence in food and drink be consistent with the dose for adults for bismuth subsalicylate drug products regulated pursuant to the recently finalized Anti-Diarrheal OTC Drug Monograph for the relief of common and traveler’s diarrhea. The following dosage regimens in children 3 – 12 years old should be added and adult dose should remain as follows:**

Age	Pepto-Bismol Regular Dose Regimen (take every half-hour to one hour as needed up to a maximum of 8 doses in a 24 hours period)	Pepto-Bismol Max Strength Dose Regimen (take every hour as needed up to a maximum of 4 doses in a 24 hour period)
3 - 6 years	131 mg	262 mg
6 – 9 years	175 mg	350 mg
9 – 12 years	262 mg	525 mg
>12 years (adults)	262 mg	525 mg

The directions above are supported by the fact that children under 12 years of age experience the same incidence of upset stomach as adults. A consumer research study (Study # MRD 83274, The Procter & Gamble Co., see report in Appendix 3) compared the age dependence of upset stomach experience. In this study, a US nationally representative sample of 450 households maintained diaries of stomach symptoms experienced by all family members during a two-week period.

Results of this study are as follows:

	<u>Age (years)</u>				
	<u>&lt; 12</u> N = (625)	<u>13 – 18</u> (252)	<u>19 – 34</u> (921)	<u>35 – 50</u> (854)	<u>&gt;50</u> (1,302)
% of individuals experiencing upset stomach	8	10	8	7	5

Another consumer research study (Study # PD 0292-07, The Procter & Gamble Co., see report in Appendix 4) showed that upset stomach is attributed to overindulgence in food and drink for children and adults. This study, conducted in a US nationally representative sample of 159 parents completing a mail-back, self-administered questionnaire, asked parents the cause of upset stomach experienced by themselves and their children aged 3 – 12 years. Results of this study, shown in the following table, showed that statistically ( $p < 0.05$ ) the cause of upset stomach is as likely to be attributed to overindulgence in food and drink for children in this age group as for adults.

	<u>Children (3 – 12 years)</u>	<u>Adults (≥ 18 years)</u>
% of individuals whose upset stomach was attributed to overindulgence in food and/or drink	33	43

The same consumer study also showed that bismuth subsalicylate (Pepto-Bismol®) is used by a majority of parents to treat upset stomach in their children aged 3 – 12 years. Additionally, significantly more parents ( $p < 0.05$ ) cited using Pepto-Bismol® than other stomach remedies.

Results of these consumer studies demonstrate that 1) children ages 3 – 12 experience the symptoms of upset stomach at similar rates to adults, 2) overindulgence in food and drink are frequent causes of upset stomach in children aged 3 – 12 years, and 3) bismuth subsalicylate is widely used to treat upset stomach in children 3 – 12 years old.

3. **Combination drugs**

**Procter & Gamble continues to recommend that the FDA include combination upset stomach/antiflatulant drugs containing bismuth subsalicylate and simethicone in the overindulgence monograph for the relief of gas and upset stomach due to overindulgence in food and drink.**

Consumer studies show that combining the active ingredients bismuth subsalicylate and simethicone, in doses designated in their respective monographs, does not decrease the safety or effectiveness of any of the individual active ingredients. Studies conducted a bismuth subsalicylate plus simethicone combination drug showed reduction of foam height in an *in vitro* test (*in vitro* foam reducing capacity test: Pepto-Bismol with simethicone, The Procter & Gamble Co., see synopsis in Appendix 5). These data demonstrate that bismuth subsalicylate does not decrease the foam-reducing capacity of the simethicone active ingredient.

Bismuth subsalicylate and simethicone in combination, when used under adequate directions for use and warnings against unsafe use, provide rational concurrent therapy for a significant proportion of the target population. A consumer study of 159 adults (Study # PD 0292-07, The Procter & Gamble Co., see report in Appendix 4) showed that gas frequently occurs concurrently with the symptoms for which bismuth subsalicylate has been shown to be effective.

The results of this study are outlined below:

<u>Adults who stated they experience gas with the following symptoms:</u>	<u>%</u>
Diarrhea	62
Fullness/bloating	57
Upset stomach	55
Indigestion	44
Heartburn	24

When used under adequate directions for use and warnings against unsafe use specified in the monographs for each active ingredient, a bismuth subsalicylate and simethicone combination drug would, therefore, provide rational concurrent therapy for a significant proportion of the target population (upset stomach/indigestion sufferers).

Also, per the Agency's telephone request, within this submission are all references that were cited in the original submission by Procter & Gamble, dated April 21, 1992. A listing of the literature citations and their location in the References section of this submission may be found at the conclusion of this letter.

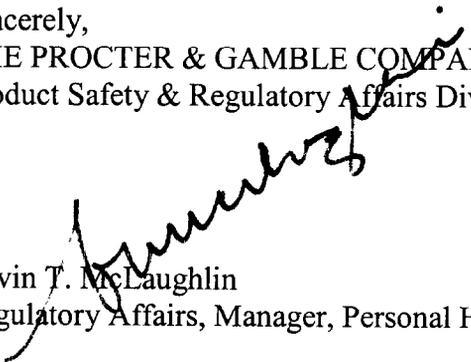
*Procter&Gamble*

In conclusion, Procter & Gamble respectfully requests that the Agency give full consideration to the data supplied pursuant to its OTC Monograph review of bismuth subsalicylate. We further request that the Agency give consideration to Procter & Gamble's renewed recommendations presented in this letter. Procter & Gamble gratefully acknowledges the time and effort expended by the Agency in the review of the information to be incorporated into the monograph.

Additionally, this submission contains certain commercial trade secrets regarding proprietary consumer study methodologies, therefore, pursuant to 21 CFR 20.61, we request all data contained in Appendices 1 – 5 (Volumes 2-4) of this submission remain confidential and not made available to the public.

If you have questions concerning the information provided, please contact the undersigned at (513) 622-2420.

Sincerely,  
THE PROCTER & GAMBLE COMPANY  
Product Safety & Regulatory Affairs Division



Kevin T. McLaughlin  
Regulatory Affairs, Manager, Personal Health Care

Encl.

***Procter&Gamble***

This submission contains the following items:

<b>Item</b>		<b>Volume</b>
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Appendix 1	Home Performance Test Report PD # 0390-54 Consumer Definition of Stomach Discomfort Symptoms	2
Appendix 2	Summary Report PD # 1083-53, G.I. Symptom Mapping Research	2
Appendix 3	Symptom Screening Study for Illness Diary Report MRD # 83274	3 - 4
Appendix 4	Home Performance Test Report PD # 0292-07 Stomach Discomfort Indices Children Ages 3 – 12	4
Appendix 5	Synopsis results of <i>in vitro</i> Foam Reducing Capacity; Laboratory Notebook HH-0736 Results	4

**References**

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10. Report of Scientific Advisory Group meeting on bismuth subsalicylate pediatric dosing for the treatment of acute diarrhea. Procter & Gamble. 1991.
11. Lukacovic M.F., Watters K.J., Bioavailability study with Pentagastrin – Pepto-Bismol with simethicone. PBDB # 14. Procter & Gamble. 1992.
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