Procter & Gamble

The Procter & Gamble Company
Health Care Research Center
8700 Mason-Montgomery Road, Mason, Ohio 45040-9462

July 16, 2003

Dockets Management Branch (HFA - 305)
U.S. Food and Drug Administration
Room 1061
5360 Fishers Lane
Rockville, MD 20852

Re: Docket Nos. 93N-0182 and 82N-0166
Labeling of Oral and Rectal Over-the-Counter Drug Products Containing Aspirin and Nonaspirin Salicylates; Reye's Syndrome Warning [21CFR 201], Federal Register Vol. 68, No. 74

Dear Sir or Madam:

The Procter & Gamble Company (Procter & Gamble) herewith submits, in triplicate, comments in response to the final rule: labeling of oral and rectal over-the-counter (OTC) drug products containing aspirin and nonaspirin salicylates; Reye's syndrome warning, published on April 17, 2003 in the Federal Register (Vol. 68, No. 74, pages 18861-18869). Procter & Gamble, as a manufacturer and distributor of OTC drug products containing nonaspirin salicylates, is directly affected by this final rule.

The proposed warning for OTC drugs containing nonaspirin salicylates including bismuth subsalicylate states:

> "Reye's syndrome: Children and teenagers who have or are recovering from chicken pox or flu-like symptoms should not use this product. When using this product, if changes in behavior with nausea and vomiting occur, consult a doctor because these symptoms could be an early sign of Reye's syndrome, a rare but serious illness."

Procter & Gamble has previously submitted comments to Reye's syndrome labeling proposals (see attached comments to Docket No. 93N-0182 dated December 17, 1993 [Attachment 1] and July 1, 1993 [Attachment 2]). The above warning is consistent with our previous comments.

A similar warning has been voluntarily included by Procter & Gamble in labeling for its Pepto-Bismol ® products, which contain bismuth subsalicylate, since 1992.

We (Procter & Gamble) acknowledge FDA's statement:

> "Mandating warnings in an OTC monograph does not require a finding that any or all of the OTC drug products covered by the monograph actually caused an adverse event and the FDA does not so find..." (FR Vol. 68, No. 74, pg. 18867, col. 1).

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82N-0166

As presented in FDA's response to comments (comment I, FR Vol. 68, No 74, pg. 18863, col. 3), we (Procter & Gamble) agree there is no definitive evidence that drugs containing nonaspirin salicylates significantly increase the risk of Reye's syndrome.

We also support the FDA's determination that the above warning should limited to aspirin and nonaspirin salicylate active ingredients, not inactive ingredients:

> "Therefore, the agency does not have sufficient data and information at this time to require a Reye's syndrome warning on OTC drug products containing salicylates as inactive ingredients." (Federal Register [Vol. 68, No. 74, pages 18864, col. 2]).

Sincerely, The Procter & Gamble Company
Product Safety and Regulatory Affairs Department

Paul L. Bryant, Ph.D

P. LaMont Bryant, Ph.D.
Regulatory Affairs Manager
Personal Health Care R&D
Telephone: (513) 622-1830

Attachment 1.

Procter & Gamble

The Procter & Gamble Company
Health Care Research Center
8700 Mason-Montgomery Road, Mason, Ohio 45040-9462

December 17, 1993

Dockets Management Branch (HFA - 305)
U.S. Food and Drug Administration
Room 1 - 23
12420 Parklawn Drive
Rockville, MD 20857

Re: Docket No. 93N-0182
Labeling of Oral and Rectal Over-the-Counter Drug Products Containing Aspirin and Nonaspirin salicylates; Notice of Proposed Rulemaking [21CFR201], 58 Federal Register 201

Dear Sirs,

The Procter & Gamble Company (Procter & Gamble) herewith submits, in triplicate, comments in response to the proposal, published in the Federal Register October 20, 1993, to revise the Reye syndrome warning required for oral and rectal over-the-counter (OTC) human drug products containing aspirin, and also require the warning on OTC drug products containing non aspirin salicylates. Procter & Gamble, as a manufacturer and distributor of drug products for over-the-counter human use covered by this amendment, is directly affected by this proposal.

The proposed warning states:

> "WARNING: Children and teenagers who have or are recovering from chicken pox, flu symptoms or flu should NOT use this product. If nausea, vomiting or fever occur, consult a doctor because these symptoms could be an early sign of Reye syndrome, a rare but serious illness."

This same warning was also proposed as an amendment 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 (OTC) human use, published in the Federal Register May 5, 1993. [21CFR357, 58 Federal Register 85. Docket No. 82N-0166]. The Procter & Gamble Company submitted comments to this proposal July 1, 1993. We request that FDA consider Procter & Gamble's July 1 comments as part of their decision on the current proposal for drug products containing aspirin and nonaspirin salicylates.

As stated in our July 1, 1993 comments, Procter & Gamble agrees with FDA's proposed warning (with certain changes noted in comment 4, below) **provided it is limited to nonaspirin drugs which could be used to self-treat symptoms which may be an early sign of Reye syndrome**. This is because any attempt to self-treat such symptoms may delay consumers from seeking prompt medical attention, and such delay could result in increased risk if Reye syndrome is present. We continue, however, to disagree with the rationale presented for such a warning based on the presence of non aspirin salicylate, for the reasons discussed in comment 1, below.

Comment 1. There are no data to support an association between non-aspirin salicylates and Reye syndrome.

a) *FDA concluded in the final rule for the labeling of oral and rectal OTC aspirin and aspirin-containing drug products (June 9, 1988) that there are insufficient data to support requiring a Reye syndrome warning for non-aspirin salicylates. There are no new substantive data since 1988 to change that conclusion.*

We have previously addressed the issue of association of Reye syndrome with salicylates in our submission (see comments submitted by Procter & Gamble July 1, 1993 to Docket 82N-0166, copy attached). The conclusions reached in our submission were the same as those reached by the Public Health Service Reye Syndrome Task Force following their review of all available data in February 1987. No association of Reye Syndrome with salicylates in general has ever been scientifically established. No new compelling evidence has been published since the comprehensive FDA review to change that position.

b) *Unlike aspirin, there is no epidemiologic evidence of an association between use of non-aspirin salicylate and Reye syndrome.*

Epidemiology studies capable of detecting the association of aspirin with the onset of Reye syndrome have failed repeatedly to find a similar association with non-aspirin salicylates such as bismuth subsalicylate, even though the use of these non-aspirin salicylates is widespread. A summary of epidemiology studies reviewed can be found in sections I, II and III of the attachment to the comments submitted by Procter & Gamble July 1, 1993 to Docket 82N-0166 (copy attached).

In addition, the epidemiology of Reye Syndrome argues strongly against the involvement of any other salicylate other than aspirin. Salicylates other than aspirin have remained in widespread use, and many have grown in use, while the reported incidence of Reye syndrome has plummeted to such low levels that the CDC no longer publishes annual figures. The single case reports cited in the proposed regulation for bismuth subsalicylate, calcium salicylate and choline salicylate do not support a relationship between Reye syndrome and non-aspirin salicylates. Further, the referenced comment from the National Reye's Syndrome Foundation that the aspirin Reye syndrome warning should be extended to all salicylate-containing drug products is not supported by any data.

The Agency's proposal cites a report of one death associated with the use of bismuth subsalicylate. This report has been known by the agency since 1989, but to our knowledge, contains no information on whether bismuth subsalicylate was taken before or after the onset of Reye syndrome, or the validity of the diagnosis of Reye syndrome.

c) *There is no evidence that mitochondrial injury seen in the presence of salicylates <u>in-vitro</u> is relevant to the pathogenesis of Reye syndrome in humans.*

The proposed regulation (Federal Register 58 (201) p54228) refers to studies demonstrating swelling of mitochondria following <u>in vitro</u> exposure to salicylate. The proposed regulation suggests that these studies support requiring Reye syndrome warning labeling on all salicylate containing products. However, the hypothesis that mitochondrial swelling caused by salicylates is related to Reye syndrome has no scientific basis, and is not supported by the references cited.

Pranzatelli, et al, (1987) state "Demonstration of characteristic fatty infiltration and mitochondrial ultrastructural abnormalities by liver biopsy may not be specific..... or required for typical cases [of

Reye syndrome]" The same authors also state that "Attempts to demonstrate a serum factor causing mitochondrial injury from the sera of Reye syndrome patients have been unsuccessful" and go on to state that chronic salicylism, a condition of high levels of circulating salicylates, can be distinguished from Reye syndrome in part by a lack of effect on hepatic mitochondria. Review of Trauner's paper (1988) on the effect of co-administered influenza B virus on the ability of mouse mitochondria to oxidize fatty acids in vitro also concludes that "the role of salicylates in this disorder (Reye Syndrome) remains unresolved".

While the studies by Martens (1984), and Yoshida (1988), demonstrate that salicylates inhibit the oxidation of fatty acids in mitochondria in vitro, no evidence is presented that these observations are relevant to the pathogenesis of Reye syndrome. Furthermore, as pointed out by Martens, other commonly available agents such as Ca^{2+} have also been shown to cause mitochondrial swelling, but have not been epidemiologically associated with Reye syndrome. This observation is supported by other authors, such as Lehninger, A.L., *Physiol. Rev.* 42, 467 (1962), and Chappell, J.B. and Greville, G.D., *Biochem. Soc.. Symp.* 23, 39 (1963), who report that inorganic phosphate, zinc, fatty acids, ascorbate, thyroxine, glutathione, ACTH, insulin, digitoxin and growth hormone also cause mitochondrial swelling in vitro.

d) *The acetylation mechanism of action of aspirin which is not shared by non-aspirin salicylate drugs is likely to be responsible for the observed association between aspirin and Reye syndrome.*

Important chemical differences between aspirin and non-aspirin salicylate explain why these agents have different effects in the body and why the association found between aspirin and Reye syndrome should not be extrapolated to non-aspirin salicylate. No mechanism has been determined for the reported association of aspirin with Reye syndrome, and there are no scientific data to suggest that salicylate is the responsible agent. It is known that the acetyl group in acetylsalicylic acid is responsible for many effects that distinguish aspirin from non-aspirin salicylates. Because of the biological importance of these effects, if the statistical association between aspirin and Reye syndrome is real or causal, then one can reasonably conclude that acetylation by aspirin, not the salicylate from hydrolysis, is likely to be responsible for that association. A summary of mechanism of action reports can be found in section IV of the attachment to the comments submitted by Procter & Gamble July 1, 1993 to Docket 82N-0166 (copy attached).

e) *The presence of salicylates in common foods make it even less scientifically plausible that there is any association between Reye syndrome and non-aspirin salicylate exposure.*

Salicylates are widely present in foods and no association with Reye syndrome and ingestion of salicylate-containing foods has been determined. Data on salicylate exposure from foods is presented in section V of the attachment to the comments submitted by Procter & Gamble July 1, 1993 to Docket 82N-0166 (copy attached).

Comment 2. The purpose for a warning referring to Reye syndrome on Pepto-Bismol is totally different from that on aspirin, and thus the use of the same warning is potentially misleading.

The presence of a voluntary warning referring to Reye syndrome on the label of Pepto Bismol has an entirely different purpose than the Reye syndrome warning on aspirin products. The warning required for aspirin-containing products is prompted by the possibility that the use of aspirin could increase the risk that Reye syndrome will develop. The warning on Pepto-Bismol is not prompted by a concern that the non aspirin salicylate in the product might be a risk factor for Reye syndrome in susceptible individuals.

Instead, the label warns against the use of the drug to treat symptoms such as nausea or vomiting which may be early signs of Reye syndrome. Any attempt to self-treat such symptoms may delay consumers from seeking prompt medical attention, and such delay could result in increased risk if Reye syndrome is present.

The basis for the warning on aspirin-containing drugs was an epidemiologic association with Reye syndrome. In fact, the final rule for aspirin-containing drugs states that "reported to be associated with aspirin" wording was added to reflect a large, statistically significant association between Reye syndrome and the ingestion of aspirin during chicken pox and flu. Since no such association has been shown for non-aspirin salicylates, such as Pepto-Bismol, it is not appropriate for the two different types of drugs to carry the same warning, since this could mislead and confuse consumers.

Comment 3. Requiring a Reye syndrome warning on all drugs containing salicylates would reduce its effectivity.

Salicylates are commonly used as inactive ingredients in many OTC drugs. For example, methyl salicylate is widely used as a peppermint flavor in mouthwash, toothpaste and cough medications. Requiring a Reye syndrome warning for all drugs containing salicylates would require this warning on huge number of drugs, and reduce effectivity of warning on those drugs, such as aspirin, which have been shown to be associated with Reye syndrome. There would also be a significant economic impact in the cost of relabeling drugs containing salicylates as inactive ingredients.

Comment 4 The warning for non aspirin drugs which could be used to treat symptoms which may be an early sign of Reye syndrome should be modified by deleting the words "flu symptoms" and "fever".

The warning, as modified, should read:
"WARNING: Children and teenagers who have or are recovering from chicken pox or flu should NOT use this product. If nausea or vomiting occur, consult a doctor because these symptoms could be an early sign of Reye syndrome, a rare but serious illness."

a) *"Flu symptoms" is redundant and should be deleted.*

Since Procter & Gamble submitted comments July 1, 1993, to the proposed warning for orally administered drug products for relief of symptoms associated with overindulgence in food and drink for over-the-counter (OTC) human use [Docket No. 82N-0166], we have reconsidered the appropriateness of the term "flu symptoms". We now recommend that the warning proposed for the overindulgence drug tentative final monograph be amended to delete the term "flu symptoms". We share FDA's desire to make the warning as simple and easy to understand as possible.. As such, adding the term "flu symptoms" to "flu" is redundant and is likely to be confusing to consumers.

The purpose of this portion of the warning is to identify the prodromal illnesses which may precede development of Reye syndrome. Even if some consumers could differentiate between the illness and its symptoms, the warning applies to recovery from the illness itself, just as it applies to recovery from "chicken pox" and not "chicken pox symptoms". We believe this simpler warning is the most easily understood by consumers. We request that FDA consider this comment, together with those submitted by Procter & Gamble on July 1, 1993 (copy attached), when determining the appropriate warning for drugs to treat overindulgence symptoms.

b) Fever is not a common symptom of Reye syndrome and should be deleted.

In addition to the commonly recognized Reye syndrome symptoms of nausea and vomiting, the proposed warning includes "fever" as a symptom of Reye syndrome. Our careful review of the medical literature did not identify fever as a common symptom. We request that FDA consider removing the word "fever" from the proposed warning (see references provided by Procter & Gamble July 1, 1993, copy attached).

We respectfully request that the Agency give full consideration to the comments and recommendations presented in this letter, and we gratefully acknowledge the time and effort expended by the Agency in the review of the information to be incorporated in the monograph. If you have questions concerning the information provided, please contact the undersigned at (513) 626-1402.

Sincerely.
The Procter & Gamble Company
Regulatory and Clinical Development Division

Pamela M. Sinnott
Regulatory Affairs Manager

Attachment 2.

Procter & Gamble

The Procter & Gamble Company
Health Care Research Center
8700 Mason-Montgomery Road, Mason, Ohio 45040-9462

July 1, 1993

Dockets Management Branch (HFA - 305)
U.S. Food and Drug Administration
Room 1 - 23
12420 Parklawn Drive
Rockville, MD 20857

Re: Docket No. 82N-0166
Orally Administered Drug Products for Relief of Symptoms Associated with Overindulgence in Food and Drink for Over-the-Counter Human Use; Proposed Amendment to the Tentative Final Monograph [21CFR357], 58 Federal Register 85.

Dear Sirs,

The Procter & Gamble Company (Procter & Gamble) herewith submits, in triplicate, comments in response to the proposed amendment 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 (OTC) human use, published in the Federal Register May 5, 1993. Procter & Gamble, as a manufacturer and distributor of drug products for over-the-counter human use covered by this amendment, is directly affected by this proposal.

The proposed warning for over-the-counter drugs containing bismuth subsalicylate states:

> **"WARNING: Children and teenagers who have or are recovering from chicken pox, flu symptoms or flu should NOT use this product. If nausea, vomiting or fever occur, consult a doctor because these symptoms could be an early sign of Reye syndrome, a rare but serious illness."**

We believe that the proposed warning does not differ significantly from the voluntary warning statement currently included in the Pepto-Bismol® labeling, which states:

> **"WARNING: Children and teenagers who have or are recovering from chicken pox or flu should not use this medicine to treat nausea or vomiting. If nausea or vomiting is present, consult a doctor because this could be an early sign of Reye Syndrome, a rare but serious illness."**

With the exception of the word "fever", as discussed in comment 2, below, Procter & Gamble agrees with the wording of FDA's proposed warning statement. We do, however, disagree with the reasoning presented in the preamble to the proposed regulation for requiring such a warning. The rationale for including a warning on OTC drug products indicated for relief of overindulgence symptoms is to discourage attempts to self-treat symptoms which may be early signs of Reye syndrome. The need for such a warning is not due to the presence of non-aspirin salicylates in these products, as explained in comment 1, below.

We also disagree with the preamble statement regarding the recommendations of the July 1991 Gastrointestinal Drugs Advisory Committee. Specifically, there was no recommendation from that Advisory Committee meeting that products containing bismuth subsalicylate should have a stronger warning regarding Reye syndrome. Rather, that opinion was expressed by only one committee member, and was not adopted by the Advisory Committee itself. Procter & Gamble respectfully requests that the incorrect preamble statements in this proposed regulation with respect to the conclusions of the Gastrointestinal Drugs Advisory Committee recommendations be corrected when this rule is published in final form.

Comment 1. The purpose for this warning differs from that for the aspirin Reye syndrome warning.

We note that the proposed warning differs significantly from the warning required for drugs containing aspirin, and agree that this is appropriate. The final rule for aspirin-containing drugs states that "reported to be associated with aspirin" wording in the aspirin warning was added to reflect a large, statistically significant association between Reye syndrome and the ingestion of aspirin during chicken pox and flu. However, the situation with non-aspirin salicylates is not the same as aspirin, for the following resons:

a) There are no scientific data establishing an association between non-aspirin salicylates and Reye syndrome.
Epidemiology studies capable of detecting the association of aspirin with the onset of Reye syndrome have failed repeatedly to find a similar association with non-aspirin salicylates such as bismuth subsalicylate, even though the use of these non-aspirin salicylates is widespread. A summary of epidemiology studies reviewed can be found in sections I, II and III of the attachment to this letter.

b) The acetylation mechanism of action of aspirin which is not shared by non-aspirin salicylate drugs is likely to be responsible for the observed association between aspirin and Reye syndrome.
No mechanism has been determined for the reported association of aspirin with Reye syndrome, and there are no scientific data to suggest that salicylate is the responsible agent. It is known that the acetyl group in acetylsalicylic acid is responsible for many effects that distinguish aspirin from non-aspirin salicylates. Because of the biological importance of these effects, if the statistical association between aspirin and Reye syndrome is real or causal, then one can reasonably conclude that acetylation by aspirin, not the salicylate from hydrolysis, is likely to be responsible for that association. A summary of mechanism of action reports can be found in section IV of the attachment to this letter.

c) The presence of salicylates in common foods make it even less scientifically plausible that there is any association between Reye syndrome and non-aspirin salicylate exposure.
Data on salicylate exposure from foods is presented in section V of the attachment.

Thus the reason for including a warning on drugs for relief of symptoms due to overindulgence in food and drink, such as Pepto-Bismol, is not prompted by a concern that the non-aspirin salicylate in the product might be a risk factor for Reye syndrome in susceptible individuals. Instead, the label warns against the use of the drug in children or teenagers who have, or are recovering from, chicken pox or flu, to treat symptoms such as nausea or vomiting which may be early signs of Reye syndrome. Any attempt to self-treat such symptoms may delay consumers from seeking prompt medical attention, and such delay could result in increased risk if Reye syndrome is present. Thus, this warning is not similar in its purpose to the warning required for aspirin-containing products,

which is prompted by the possibility that the use of aspirin could increase the risk that Reye syndrome will develop.

Comment 2. <u>Fever is not a common symptom of Reye syndrome.</u>

In addition to the commonly recognized Reye syndrome symptoms of nausea and vomiting, the proposed warning includes "fever" as a symptom of Reye syndrome. Our careful review of the medical literature, including references 6 and 7 cited in the proposed rule, and references V-X provided in the attachment to this letter, did not identify fever as a common symptom. In fact, the Diagnosis and Treatment of Reye's Syndrome Consensus Conference report (reference Y, provided in the attachment) specifically states under "What are the Key Symptoms?" that "neither fever nor jaundice is usually present". The report of the Consensus Conference was the source of the definition of Reye syndrome required for admission to the PHS clinical study. In addition, bismuth subsalicylate is not indicated for treatment of fever and is unlikely to be used to treat fever. We request that FDA consider removing the word "fever" from the proposed warning.

Procter & Gamble believes that it is important not to use bismuth subsalicylate, or any other OTC medicine, to self-treat symptoms which may be an early sign of Reye syndrome. We consider a warning of the type proposed by FDA to be appropriate to warn consumers about the danger of attempting to self-treat symptoms (such as nausea and vomiting), under circumstances when such symptoms may be an early sign of Reye syndrome, and delay seeking prompt medical attention.

We appreciate the fact that the Agency has adopted virtually all of the language which Procter & Gamble voluntarily placed on its Pepto-Bismol label to communicate this important information to consumers, as well as the fact that the Agency believes that this wording "is more informative than the wording currently used in the aspirin warning". We respectfully request that the Agency give full consideration to the comments and recommendations presented in this letter, and we gratefully acknowledge the time and effort expended by the Agency in the review of the information to be incorporated in the monograph. If you have questions concerning the information provided, please contact the undersigned at (513) 626-1402.

Sincerely.
The Procter & Gamble Company
Regulatory and Clinical Development Division

Pamela M. Sinnott
Regulatory Affairs Manager

ATTACHMENT

PROCTER & GAMBLE
COMMENTS ON FDA REYE SYNDROME WARNING PROPOSAL

I. EPIDEMIOLOGIC STUDIES

No association has been found between non-acetyl salicylic acid (non-ASA) salicylates and Reye syndrome (RS) through epidemiological studies.

1. PHS Studies.

Pilot Study. The publication titled "Public Health Service Study On Reye's Syndrome And Medication: Report of the Pilot Phase" includes 30 case-patients. Of these cases, 28 were exposed to ASA alone and 1 case was exposed to bismuth subsalicylate alone. Two controls were exposed to both ASA and bismuth subsalicylate. (The publication of the Pilot Phase appears as Appendix A.)

Main Study. The published report of the Public Health Service (PHS) Study of Reye's Syndrome and Medications (Main Study) concluded that "Analysis of the independent risk of aspirin and nonaspirin salicylates revealed a significant association with aspirin (odds ratio, 26; lower 95% confidence limit, 6.4); the independent risk of nonaspirin salicylates could not be assessed because only two cases were not exposed to aspirin." Of the patients who did not take ASA, one case-patient took bismuth subsalicylate, and one case-patient reported to have taken salicylate was found upon further review of the case reports not to have taken any form of salicylate. However, in the control group, 11 subjects who did not take ASA took bismuth subsalicylate and two took magnesium salicylate. Twenty five of the case-patients took ASA. If one looks at all patients (including those that took both ASA and non-ASA salicylates), 19% of the case patients and 14% of the controls took non-ASA salicylates with no significant difference between groups. (The publication of the Main Study appears as Appendix B.)

2. Ohio Department of Health Study.

An Ohio Department of Health study has been interpreted in the past as demonstrating an association between salicylates in general and RS. However, because of a variety of discrepancies in its conduct and statistical analyses, this study and the conclusions drawn from it are considered by independent authorities to be seriously flawed. The PHS studies discussed above were conducted to help address the issues and limitations of the Ohio and earlier studies. Re-analyses of data from it by groups including the Biometric Research Institute (see II, 2, below) show no evidence whatsoever to suggest an association between non-ASA salicylates and RS. This conclusion is supported by the results of the PHS Pilot Study and Main Study, and the Yale Study (Appendix F). (The Ohio Department of Health study appears as Appendix C.)

Additionally, we fully agree with the FDA's Reye's Syndrome Working Group (47 FR 249 p 57889, Appendices D, E) that only the 64 cases and controls in the last half of the Ohio study offer sufficient day-to-day symptom and medications records to permit analyses for association of drug therapy with RS. These analyses were considered critical by the FDA RS Working Group because the use of a medication must have occurred before the onset of RS to be considered pertinent exposure. Thus, only the data from this group of cases and controls can legitimately be used to determine whether an association can be found with the ingestion of a medication. Analyses of these data (see II. below) found no association between non-ASA salicylates and RS. (The Federal Register Advanced Notice of Proposed Rule Making on Labeling for Salicylate-Containing Drug Products appears as Appendix D; The Introduction to the Report By Reye's Syndrome Working Group to the FDA appears as Appendix E.)

3. Yale Study.

The most carefully designed study of Reye Syndrome and its associate risk factors has been completed by the Yale University School of Medicine (JAMA, 261: 2517-2524, 1989, provided in Appendix F). In addition, this study was presented orally to the Agency and (at the Agency's request) to the Centers for Disease Control.

An exhaustive search for cases and extensive review of the prodromal medications showed that none of the 24 RS cases studied had been exposed to non-ASA salicylates. Thus, this study supports the two PHS studies and reinforces the position that no study has ever suggested an association between non-ASA salicylates and RS.

4. Other Studies.

We are aware of additional studies that have attempted to investigate the etiology of RS. These include studies done in Arizona (Starko, et al., Pediatrics, 66:859-864, 1980), Michigan (Waldman, et al., JAMA 247:3089-3094, 1982), and Australia (Orlowski et al., Pediatrics, 80:638-642, 1987, Orlowski, et al., Cleveland Clin. J. Med. 57:323-329, 1990). Exposure data collected in the Arizona and Michigan studies failed to identify the day-to-day histories of product use as these relate to the antecedent illness and RS. Therefore, we again concur with the FDA Reye's Syndrome Working Group (Appendix E) that the data reported from these studies is irrelevant to efforts to investigate causal association for RS. The 1987 Australian study reported no association between RS and ASA. The second Australian study (1990) confirmed the result of the 1987 report and added a lack of any association with any non-ASA salicylate.

II. INDEPENDENT REVIEWS OF EPIDEMIOLOGIC STUDIES

Reviews of data from epidemiologic studies by panels of independent experts have consistently found no information to suggest an association between non-ASA salicylates and RS.

1. National Academy of Sciences Institute of Medicine Reviews of PHS Pilot and Main Studies.

The Institute of Medicine (IOM) of the National Academy of Sciences reviewed the data from the Pilot and the Main studies of the Public Health Service. In its Report No. 5 on the Pilot study, IOM stated, ". . . description of an association of "salicylates" and RS is incorrect and misleading. Instead, the association should be presented as a relationship with aspirin, because there is insufficient information on the effects of salicylates in general in this study. (IOM Report No. 5 appears as Appendix G.)

The opinion that there is insufficient evidence to associate non-ASA salicylates with RS was emphasized further by IOM Report No. 6 on the PHS Main Study. While concurring with the association of aspirin with Reye syndrome, IOM stated that " . . . reporting the relative risks for 'salicylates' as the investigators have done in their report is inappropriate unless the assumption is made that the etiologic association is necessarily with the salicylate component of aspirin. There currently is insufficient evidence to support this assumption." (IOM Report No. 6 appears as Appendix H.)

2. Biometric Research Institute Review of Ohio and PHS Pilot Studies.

In a report entitled "Analysis of Exposure to Nonaspirin Salicylates Among Subjects from the Ohio Department of Health Survey and the Public Health Service Pilot Study on Reye Syndrome", the Biometric Research Institute, Inc. (BRI) concluded, "Thus, there is no epidemiological evidence that an association exists between the use of NSA (non-ASA salicylate) medications and an increased risk of developing Reye Syndrome." This independent review was performed at the request of the Proprietary Association to determine if there was evidence of an association between exposure to non-ASA salicylates and Reye Syndrome. BRI reviewed the raw data from the two studies in reaching its conclusion. (Please refer to Appendix I for the BRI report.)

3. FDA Reye's Syndrome Working Group Report.

The Reye's Syndrome Working Group concluded that studies conducted prior to the second year of the Ohio State Department of Health study were of no value in assessing the etiology of RS.

Of the reports available by May 24, 1982, the Reye's Syndrome Working Group of the FDA concluded that only the final 64 case studies (second year) of the Ohio Department of Health Survey contained data useful to assessing the association between disease symptoms and drug use. The PHS studies and the Yale study did not begin until after this date. The earlier studies, including the first year of the Ohio study, failed to obtain information on the chronological relationships between drug therapy, the antecedent disease and RS; therefore, potential meaningful associations between drug therapy and RS could not be determined. (The Introduction to the Report By Reye's Syndrome Working Group to the FDA appears as Appendix E.)

III. PREVIOUS FDA DETERMINATIONS

FDA concluded in 1988 that there is no scientific basis for requiring RS warning labeling on non-ASA salicylate-containing drug products. Following review of available data, the FDA issued a final rule, on June 9, 1988, to extend its requirement for Reye Syndrome labeling of oral and rectal ASA and ASA-containing products. The warning required for aspirin-containing drugs states, in part, "....Reye syndrome, a rare but serious illness reported to be associated with aspirin" (21CFR201.314). The preamble to the final rule states that "reported to be associated with aspirin" wording was added to reflect the PHS study finding of a large, statistically significant association between Reye syndrome and the ingestion of aspirin during chicken pox and flu.

In concluding that RS labeling should not be extended to non-ASA salicylates, the preamble to the final rule states under *5. Other Salicylates,* "FDA notes that the scientific research to date, on which the Reye syndrome warning statement requirement is based, focuses on the association between Reye syndrome and aspirin. rather than on the broader category of drug products containing nonaspirin salicylates. Indeed, the PHS study reported that there were too few subjects with reported exposures to nonaspirin salicylates for a meaningful analysis." (The publication of the FDA final rule appears as Appendix J.)

IV. ACETYLATION IS A CRITICAL MECHANISM FOR THE MOST IMPORTANT ASA ACTIONS:

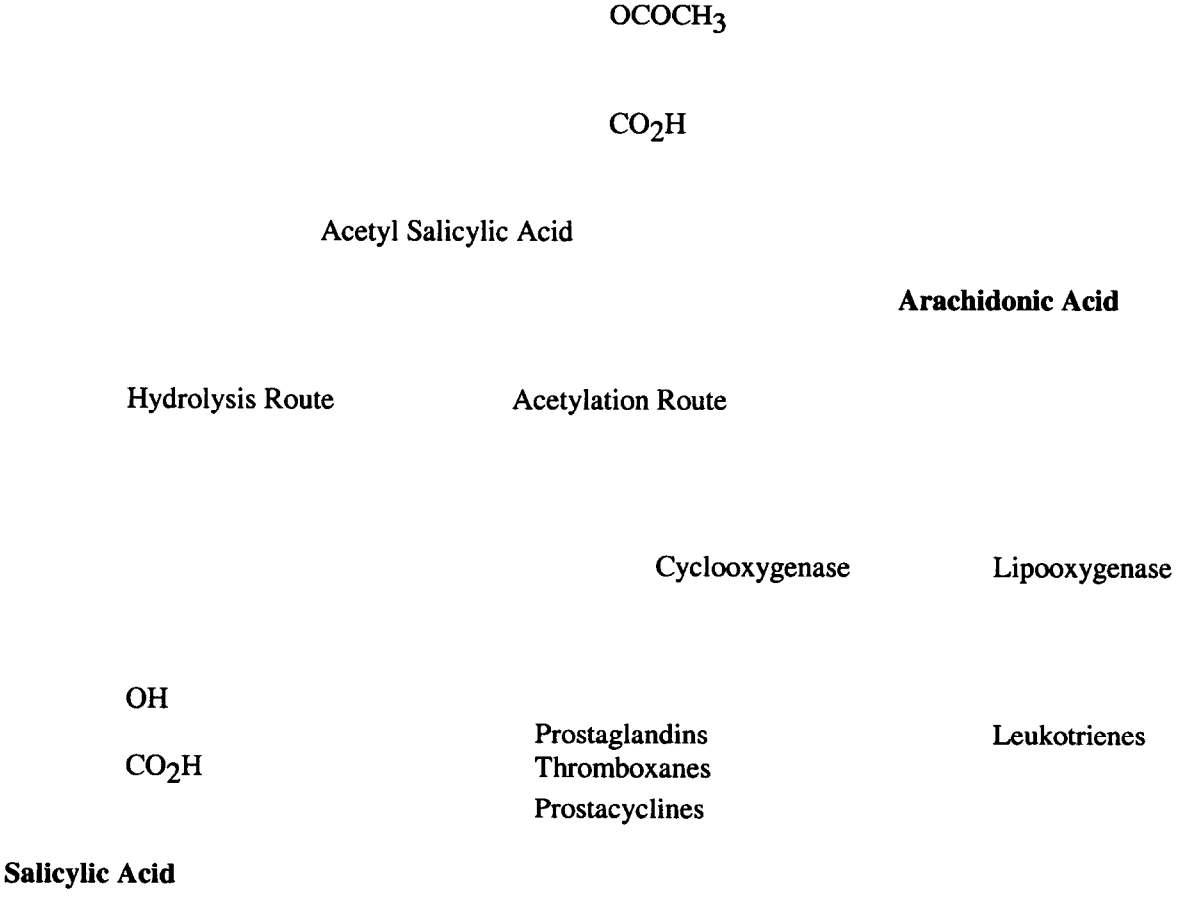
Although aspirin is metabolized by the body to salicylate, its primary physiological functions are linked to acetylation of key enzymes. The acetyl group in ASA is responsible for many effects that distinguish ASA from non-ASA salicylates. Because of the biological importance of these effects, and in view of the lack of any epidemiologic link between non-ASA and RS, if the statistical association between aspirin and Reye syndrome is real or causal, one can reasonably conclude that acetylation by ASA, not the salicylate from hydrolysis, is responsible for the association found between ASA and RS.

Any speculation that ASA association with RS is through the salicylate pathway ignores a significant pharmacological pathway of ASA -- acetylation. ASA is known to exert its effects through at least two major pathways. In the body hydrolysis results in salicylic acid which can cause the responses obtained by other salicylates in general. Concurrent with hydrolysis, however, ASA's activated acetyl group acetylates a number of important enzymes which are involved in the biosynthesis of very powerful biologic mediators. In particular, ASA reacts rapidly and irreversibly with cyclooxygenase to inactivate completely this enzyme. Cyclooxygenase plays an essential role in the normal arachidonic acid cascade in the body which yields many of its more important biologic mediators. With the cyclooxygenase pathway closed, the body is unable to synthesize important mediators such as prostaglandins, thromboxanes and prostacyclines and, in addition, the arachidonic acid metabolism route is forced through the alternate lipooxygenase catalyzed route causing an increase in the mediators related to the leukotrienes.

In investigating the distribution of ASA's acetyl group as compared with that of its salicyl moiety, Rainsford, Schweitzer and Brune concluded, in part, that " . . . the acetylation of biomolecules may be a major factor in the development of side-effects . . . and . . . in addition to acetylation of prostaglandin synthetase, the acetylation of enzymes and other biomolecules may have a much wider bearing on the biochemical changes underlying the development of these side-effects." These workers found radiolabel from the ASA acetyl group in a variety of proteins, glycoproteins and lipids in body organs. In sharp contrast, no radiolabel from the salicylate moiety was found in proteins, glycoproteins and lipids. Their work supports further the unique biochemical activity of the ASA acetyl group as compared with its salicyl group. (Rainsford, et al. is attached as Appendix K.)

As mentioned above, ASA is rapidly metabolized in the body to salicylate. In the process of this conversion, ASA acetylates other molecules (Reviews of the mode of action, clinical pharmacology, and kinetic disposition of aspirin in humans are provided in Appendices L, M, N.)

BIOLOGIC ACTIVITY OF ASA



ASA acetylates proteins. Salicylates in general cannot acetylate proteins. This difference leads to different pharmacologic traits of ASA relative to other salicylates, because there are wide-ranging biologic consequences of protein acetylation by ASA. For example:

1. Hypersensitivity to ASA. There is a syndrome of ASA intolerance in humans, characterized by asthma, rhinitis and nasal polyps (Appendix O). Sodium salicylate does not cause this syndrome. Acetylation of albumin by ASA has been suggested as an initiator of the events leading to this syndrome (Appendix P).

2. Inhibition of biosynthesis. Prostaglandins are very powerful naturally-occurring compounds which can function as mediators of biologic reactions. In this role, the various prostaglandins can affect a large number of activities in the body. A list of biologic reactions for which prostaglandins are effectors includes contraction of smooth muscle, aggregation of blood platelets, migration of leukocytes, gastric secretions and inflammation. (Articles demonstrating the acetylation function of aspirin are provided in Appendices K, P, Q.)

Cyclooxygenase is an important enzyme in the synthesis of prostaglandins. The acetylation of cyclooxygenase by ASA causes irreversible inactivation of this enzyme. Sodium salicylate is a very weak inhibitor of cyclooxygenase, and is not usually available at high enough concentration in vivo to be an effective inhibitor of this enzyme. Therefore, sodium salicylate lacks many of the effects of ASA. (Articles discussing the effect of aspirin and sodium salicylate on enzyme inhibition are provided in Appendices R, S, T.)

For example, through acetylation of blood platelet cyclooxygenase, ASA can lengthen the time necessary for blood to clot. Sodium salicylate lacks this effect. Another example is that non-ASA salicylates do not cause gastric mucosal damage (peptic ulcers) whereas ASA can. Indeed, non-ASA salicylates are used to protect against this action of ASA.

In summary, epidemiological, pharmacological and biochemical data oppose the hypothesis that metabolism of ASA to salicylate is the basis for the association between RS and ASA that has been reported in epidemiologic studies. Firstly, no association has been found between RS and non-ASA salicylates through any of the epidemiologic studies. Secondly, biochemical studies have shown that ASA evokes pharmacologic and toxicologic effects through two pathways -- acetylation and salicylate -- with the most important biochemical effects being through the acetylation pathway. Thirdly, ASA and non-ASA salicylates have been shown to have many pharmacologic and toxicologic differences that are attributable to acetylation by ASA. Therefore, there is no factual basis for speculating that salicylates in general would be associated with RS.

V. OTHER SOURCES OF SALICYLATE EXPOSURE

Non-ASA salicylates are ubiquitous in common fruits and vegetables. The typical daily intake of salicylates from common foods has been reported to be greater than the lowest dose of ASA salicylate that was associated with RS in the PHS studies.

Swain, Dutton and Truswell reported on the salicylate content of 333 food items (Appendix U). They concluded that the typical daily ingestion of salicylates from foods in Western diets ranged from about 10 mg-200 mg/day. For comparison, one case report associated with RS in the PHS study had taken only one baby aspirin (81 mg. of ASA , 53 mg of salicylate). Examples of the higher concentrations of salicylates that were reported in foods include: fresh pineapple, 2.1 mg/100 gm; tomato sauce, 2.48 mg/100 gm; canned cucumbers (Gherkins), 6.14 mg/100 gm; licorice, 9.78 mg/100 gm and peppermints (candy), 7.58 mg/100 gm. The presence of salicylates in

foods is consistent with the fact that no association has been found between non-ASA salicylates and RS in the epidemiologic studies. It is also noted that non-ASA salicylate is commonly added to food products and to oral drugs as inactive ingredient. (A list of the salicylate content of 333 food items is provided in Appendix U.) This presence of salicylates in foods makes it even less scientifically plausible that there is any association between Reye Syndrome and non-aspirin salicylate exposure.

VI. CONCLUSIONS

The above discussion has presented data from several recent epidemiologic studies. Reviews of data from these studies by independent expert groups (i.e., the National Academy of Science Institute of Medicine, the Biometric Research Institute, the Reye's Syndrome Working Group of the FDA, and the FDA) concluded unanimously that no association had been found between non-ASA salicylates and RS. It is on these data and reviews that the FDA in July 1988 reaffirmed its position not to require non-ASA salicylates to carry an RS warning.

The literature also fully establishes that the most important biologic and pharmacologic effects of ASA are through its acetylation pathway. This pathway is not a property of the unacetylated non-ASA salicylates. This fact in combination with the absence of epidemiologic data to associate non-ASA salicylates with RS strongly contradicts any unfounded speculation that salicylates in general should be considered involved in the etiology of RS.

Finally, data that show the widespread presence of naturally-occurring salicylates in foodstuffs and the use of salicylates as components of manufactured foods, strongly suggest that non-ASA salicylates are not risk factors for the development of RS.

PROCTER & GAMBLE
COMMENTS ON FDA REYE SYNDROME WARNING PROPOSAL

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