DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 201

[Docket No. 82N-0158]

Labeling for Salicylate-Containing Drug Products

AGENCY: Food and Drug Administration.

ACTION: Advance notice of proposed rulemaking.

SUMMARY: The Food and and Drug Administration (FDA) is considering proposing to require certain over-the-counter (OTC) and prescription saliciylate-containing drug products for human use to bear a warning against the use of the products for the treatment of flu or chickenpox in children or adolescents under 16 years of age, because salicylates may be associated with the development of Reye syndrome (RS) in this age group. This advance notice describes the recent studies reporting an association between salicylate use and the development of RS and discusses various criticisms of these studies. This advance notice also discusses specific warning statements under consideration by the agency. FDA is publishing this advance notice so that the agency will have the benefit of a broad range of views early in the rulemaking process, and so that all interested persons will have an opportunity to express their opinions.

DATE: Comments by February 28, 1983.

ADDRESS: Written comments to the Dockets Management Branch (HFA-305), Food and Drug Administration, Rm. 4-62, 5600 Fishers Lane, Rockville, MD 20857.

FOR FURTHER INFORMATION CONTACT: Paul O. Fehnel, Jr., National Center for Drugs and Biologics (HFN-7), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301-443-6490.

SUPPLEMENTARY INFORMATION: FDA is considering whether to propose a rule that would require, among other things, that the labeling of certain salicylate-containing OTC and prescription drug products for human use bear a warning that salicylates should not be used in persons under 16 years of age with flu or chickenpox. FDA is considering this action because of recent studies reporting that the use of salicylates to treat these conditions is associated with the development of RS. The products under consideration for bearing a warning are: (1) systemically absorbed OTC salicylate-containing drug products for human use that are administered orally or rectally; and (2) systemically absorbed prescription salicylate-containing drug products for human use that are administered orally, rectally, or parenterally. The agency invites comments on any matter relevant to the proposed rulemaking being considered.

I. Background

A. *Reye syndrome.* RS is a disease of unknown cause that is characterized by severe vomiting and irritability or lethargy which may progress to delirium and coma. The illness is described clincially as having an acute onset in which the initial symptom is usually vomiting, which may be profuse and persistent, and which is often accompanied by a change in mental status. The Centers for Disease Control (CDC) has established an epidemiologic case definition for establishing the diagnosis of RS (Ref. 1). In addition, for purposes of management and study, a system of classifying the symptoms of RS into stages has been developed. The stages are zero to V, with V exhibiting the most severe symptoms.

The disease is classically described as occurring in a child or adolescent during the course of or while recovering from a mild respiratory tract infection, influenza, chickenpox, or other viral illness (Refs. 2, 3, and 46). (The illness occurring before RS may be referred to as the antecedent illness.) Influenza and chickenpox are the most commonly associated viral illnesses. The estimated incidence of RS is 0.37 to 4.7 per 100,000 persons under 18 years of age (Ref. 2), but its incidence may be 30 to 60 per 100,000 persons under 18 years of age (Ref. 2), but its incidence may be 30 to 60 per 100,000 in children of that age who have contracted influenza B (Ref. 3). CDC estimates that RS affects 600 to 1,200 children in the United States each year. A careful analysis of RS cases indicates that it is primarily observed in children between 6 months and 15 years of age (Ref. 3). The age distribution of the disease appears to depend on the type of the antecedent illness. Chickenpox-associated RS is found mainly in the 5- to 9-year age group; influenza B-associated RS is seen mainly in the 10- to 14-year age group (Ref. 3).

The mortality rate is high. In the past several years, the case fatality rate reported to CDC has been between 20 and 30 percent (Refs. 1 and 21). Permanent brain damage occurs in many other cases (Ref. 2).

RS was first described by the pathologist Douglas Reye of Australia in 1963 (Ref. 4). Subsequently, there has been substantial interest in monitoring the occurence of the disease and in attempting to identify causative factors. CDC first initiated nationwide surveillance for the disease in December 1973, in an effort to monitor its incidence during an anticipated epidemic of influenza. In December 1976, CDC and State health departments again intensified surveillance, and have been continuously maintaining surveillance since that time. Since 1976, between 200 and 500 patients per year meeting the CDC case definition have been reported to that agency. As in most disease surveillance systems, reported cases are recognized to represent only a fraction of the actual total, but increases in the number of reported cases have been observed during years of major influenza B and influenza A activity in 1977, 1979, and 1980.

Due in part to the rapid onset of RS, it has been suggested that a toxic agent interacting with the viral infection may be a causative factor in the production of the disease. Suspected agents have included environmental toxins and common medications. In its November-December 1976 *Drug Bulletin,* FDA reported a recommendation of its Neurologic Drugs Advisory Committee against the use of antiemetics, aspirin, and acetaminophen in children whose signs and symptoms indicate RS (Refs. 5 and 6).

A number of investigators have suggested the possiblility that RS may be associated with salicylates. In 1962, before Reye's initial report, Mortimer reported on four cases of fatal varicella (chickenpox) infections associated with hypoglycemia. Mortimer postulated that salicylates may have caused the hypoglycemia and the subsequent unexpected severe illnesss (Ref. 7).

In 1964, Utian reported 14 cases of what appeared to by RS and considered salicylate intoxication as a possible cause of the illness in these children (Ref. 8). In 1965, Giles suggested that a direct association existed between RS and salicylates and that in RS patients an enzyme system involving carbohydrate metabolism might by hypersensitive to salicylate (Ref. 9). In 1968, Norman reported a case of biopsy-confirmed RS associated with isolation of influenza B from the liver (Ref. 10). This patient was on long-term salicylate therapy for juvenile arthritis.

In the 1970's, several authors discussed the distinction between RS and acute salicylate intoxication. Evidence to suggest that RS and salicylism (salicylate intoxication) may be biochemically distinct was reported by Hilty in 1974 and updated in 1981 by Romshe and Hilty (Refs. 11 and 12). Hilty suggested that RS can be

distinguished from salicylism and other causes of hepatic damage by quantitative analysis of serum amino acids.

Several descriptive studies and two case-control studies examining medication histories of patients with RS were published in the 1970's. Among the studies that reported detailed information on aspirin use, the aspirin use ranged from 53 to 100 percent. The highest rates were reported in studies where information was more likely to be complete. For example, studies involving extensive home interviews found a higher prevalence of salicylate use amont RS patients. Aspirin was the only medication received by all RS patients interviewed by Reynolds, but because the doses were not considered to be excessive, the association was not emphasized (Ref. 13). In 1975, Linneman reported a history of aspirin use in 94.6 percent of 56 RS cases with known medication histories (Ref. 14).

Corey reviewed national surveillance data collected from 1973–1974 by CDC (Ref. 15). Data collection for aspirin use was based primarily on reviews on national surveillance forms supplemented in 16 percent of cases by personal communications with health personnel. In the subset of patients for whom medication history was available, 78 percent reported using aspirin. Corey expressed reservations about accuracy of the medication histories obtained through this system, noting that many patients may have erroneously reported not using aspirin.

Two case-control studies published before 1980, one conducted by Ruben (Ref. 16) and the other conducted by Corey (Ref. 17), compared medication histories of RS patients and controls. In both studies, however, interviews too place many months after the occurrence of RS, and controls were not matched for a history of illness temporally and clinically similar to cases. Medication questions, therefore, were not limited to those medications taken for the illness preceding RS in patients, or for the comparable illness in controls. Starko and colleagues (Ref. 18) were the first investigators to conduct such a study. This study is discussed below.

B. *Studies reporting an associaton between salicylates and RS.* For several years, CDC has been involved in investigations of RS. Within the past few years, four case-control studies have been conducted by the Arizona, Ohio, and Michigan State Health Departments in cooperation with CDC. The reports of these studies indicated as an association between RS and the ingestion of salicylates (e.g., aspirin) during the antecedent illness. On the basis of its review of the first three studies (Arizona, Ohio, and first Michigan study), CDC published a recommendation in the *Morbidity and Morality Weekly Report* on November 7, 1980 (Ref. 19) that "parents should be advised to use caution when administering salicylates to treat children with viral illness, particularly chickenpox and influenza-like illnesses."

A consensus development conference was held at the National Institutes of Health (NIH) in March 1981 to address diagnostic criteria and treatment of RS. Because the conference had not been called to review the first three State studies that had been recently completed at the time of the conference, data from the studies were not presented but were discussed by several participants. The conference report stated that the studies discussed at the conference indicate "an increase in the estimated relative risk of Reye's syndrome, which does not appear to be due to chance" (Ref. 46). The conference report advised that "caution in the use of salicylates in children with influenza and those with varicella is prudent." However, the report also pointed out that "certain similarities between salicylism and Reye's syndrome and those studies reporting an association between Reye's syndrome and salicylate ingestion indicate a need for further carefully designed studies before recommending changes in antipyretic therapy in children" (Reg. 46).

In November 1981, CDC convened a group of outside consultants to review the four State studies. The consultants concluded that there is "strong epidemiologic evidence for an association between the occurrence of Reye syndrome and the prior ingestion of salicylate containing medication" (Ref. 20). The consultants recommended that "until the nature of the association between salicylates and Reye syndrome is clarified, the use of salicylates should be avoided, when possible, for children with varicella infections and during presumed influenza outbreaks" (Id.). In the *Morbidity and Mortality Weekly Report* of February 12, 1982 (Ref. 21), CDC reported that the studies indicated an association between salicylates and RS and stated that "until definitive information is available, CDC advises physicians and parents of the possibility of increased risk of Reye syndrome associated with the use of salicylates for children with chickenpox or influenza-like illness."

C. *FDA review of the four State studies.* In response to the reported association between salicylates and RS, FDA formed a working group composed of members of the agency to review the available data to determine the quality and strength of the association. Despite the apparent association between salicylates and RS reported by the four State studies, the working group recognized that the studies required careful evaluation both because of the inherent limitations of case-control methodology and because of questions raised by earlier reviews of the studies. Case-control studies attempt retrospectively to assess the relationship of an existing disease or disorder to other variables or attributes, such as exposure to medications. After the initial identification of cases, that is, persons with the disease under investigation, a suitable control group of persons without the disease is identified for comparison purposes. The relationship of an attribute to the disease under investigation is examined by comparing the case group and the control group to determine how frequently the attribute is present in each group. Thus, in the RS studies, the investigators attempted to match reported cases of RS with control subjects who appeared to match the case subjects as closely as possible except for the development of RS.

The FDA working group recognized that an adequate evaluation of the four State studies would require consideration of the design and execution of the studies, including such questions as: (1) Potential differences in the type and severity of antecedent viral illness in cases and controls; (2) comparability and accuracy of the drug histories in cases and controls; (3) potential confusion as to the active ingredients in drugs administered to cases and controls; (4) potential differences in methods of collecting data for cases and controls; (5) the period of recall time and differences in the periods of recall time for cases and controls; (6) criteria used for diagnoses of RS and, especially, the criteria employed to establish the onset of RS; and (7) the reasons for the exclusion of reported RS cases from the studies.

In evaluating the available date, the FDA working group's activity included the following:

1. Review of materials available from the investigators in Arizona, Michigan, and Ohio.

2. Review of summaries provided by CDC on studies concerning RS and salicylates (Ref. 22).

3. Review of wrtitten analyses by employees or consultants of Sterling Drug (Refs. 23, 24, 25, and 26) and Schering-Plough (Ref. 27), which are two manufacturers of salicylate drug

products, and meetings with representatives of the two companies to hear presentations of these analyses by each firm (Refs. 28, 29, and 30).

4. Review of the written information presented by the Health Research Group (HRG) and meeting with representatives of HRG to hear their interpretation of the data (Refs. 31 and 32).

5. Site visits to the Michigan State Health Department and the Ohio State Health Department to obtain further details on how the studies in these States were conducted and to audit certain data from the study records (Ref. 33).

6. A meeting with scientists from CDC and National Institutes of Health, at which suggestions for analysis of the date were discussed.

The FDA working group prepared a preliminary report of its review of the four State studies and available information relating to the interpretation of these studies (Ref. 34). That report, dated May 18, 1982, presents a detailed discussion of the results of the studies and the working group's analysis of the data. The following summarizes the results of the four State studies and the working group's analysis of those studies:

1. *Arizona study.* The first reported case-control study on RS was conducted by Starko et al. in Arizona (Ref. 18). The study included 7 school children, hospitalized December 21 through 25, 1978, during an outbreak of influenza A/Brazil and 16 classmate controls who were ill during December 1978. All seven cases had recent influenza A (H1N1) infections, according to the analysis of blood samples collected. Blood samples were not collected for the control group.

The major finding of the study was that all 7 of the cases, but only 8 of the 16 controls, gave a history of salicylate ingestion during the antecedent illness for cases or during the viral illness for controls. Because the study lacked daily medication recording and had a small sample size, the working group did not attempt to conduct a more detailed analysis of the data from this study.

2. *Michigan studies.* Two case-control studies were performed by the Michigan Health Department. The first study was conducted during the months of March and April 1980 following an influenza B outbreak during the winter of 1979–1980. The second study began on September 1, 1980, and continued into 1981. Influenza A (H3N2) virus predominated during the second study. A report of these two studies has been published in the June 11, 1982 issue of the *Journal of the American Medical Association* (Ref. 35).

Under the Michigan State health code, physicians are required to report cases of RS to the State health department within 10 days. During the first study, 56 cases were reported. Twenty-five of the 56 patients were selected for the study because they lived within driving distance of the Michigan Health Department. During the second study, there were 17 cases reported; 5 of the 17 second study cases were excluded by the Michigan Health Department.

During both studies, controls were matched to cases on the basis of gastrointestinal (GI) symptoms, respiratory illness, or chickenpox. In the second study, cases and controls also were matched by temperature strata as follows: less than 100 degrees Fahrenheit, 100.1 to 102.9 degrees, and 103 degrees and over. For the cases, the date of protracted vomiting or behavioral change was established as the date of onset of RS.

In the first study, interviews with parents of children with RS were conducted an average of 45.5 days (4 to 83 days) after the onset of RS. During the second study, interviews took place an average of 4.8 days (2 to 10 days) after the onset of RS in the cases. Interviews for the control groups were conducted an average of 55.3 days (9 to 121 days) for the first study, an average of 12.2 days (3 to 40 days) for the second study.

In the first study, 24 of 25 (96 percent) cases took salicylate-containing medication before the onset of pernicious vomiting, compared to 30 of 46 (65 percent) controls. When highest measured temperature was used retrospectively to match controls to cases to attempt to ensure comparability, the difference in salicylate ingestion remained significant in that 14 of 14 (100 percent) cases as compared to 14 of 19 (73 percent) controls ($p<.05$) had ingested salicylates. During the second year of the study, 12 of 12 (100 percent) cases as compared to only 13 of 29 (45 percent) controls ($p<.002$) were reported to have received salicylate-containing medications. Medications containing acetaminophen but not salicylates were taken by 8 controls (17.8 percent) and 1 case (4 percent) in year 1 and by 9 controls (31 percent) and no cases in year 2.

Daily medication use was recorded in the second Michigan study for the 12 cases included in the study and their associated controls. This daily record was used to determine whether the cases and controls used salicylates on day 1; day 1 or 2; or day 1, 2, or 3 of their antecedent illness. The FDA working group was thus able to evaluate the apparent association between salicylate ingestion and RS using data where the salicylate use was most likely to be before the onset of RS and most likely to be in response to symptoms of the antecedent illness. Because the data sets to be analyzed consisted of cases matched to one or two controls on the basis of multiple characteristics (age, race, sex, geography, and fever), the working group employed a multiple conditional logistic analysis. That approach accounts for the variable matching to give a valid estimate of the excess risk associated with the cases and salicylate use. The multiple conditional logistic analysis showed that on day 1 of the antecedent illness, cases were 9.1 times more likely to have taken aspirin than their matched controls and that this was statistically highly significant. Because all of the cases used salicylates on days 2 and 3, this analysis could not be performed for day 1 or 2, or for day 1, 2, or 3.

3. *Ohio study.* The Ohio study was initiated under a contract from CDC in December 1978. The original study, developed by CDC investigators in cooperation with the Ohio State Department of Health, was designed to examine the possible relationship between RS and respiratory viral illnesses. The Ohio State Department of Health also wanted to conduct an exploratory investigation of other possible risk factors, including medications, environmental toxins, and a number of other variables which had been mentioned in the literature. The study was conducted from December 1978 through March 1980 and included 97 cases of RS. Thirty-three of the cases have been identified as "first year" because they were investigated before the collection of data about the development of symptoms and the administration of drugs on a day-to-day basis. The 64 cases for which such data were collected are referred to as "second year."

For both years of the study combined, the Ohio State Department of Health found that salicylates were the only medications which were taken significantly more frequently in cases (94 of 97=96.8 percent) than in controls (110 of 156=70.5 percent) before the development of symptoms of RS. Medications containing acetaminophen but not salicylates were taken by 29 of 156 (18.6 percent) controls but only 1 of 97 (1 percent) cases. Medication containing acetaminophen in combination with salicylates were taken by 16 of 97 (16 percent) cases compared to 51 of 160 (32 percent) controls ($p<0.01$).

The Ohio State University Biometry Facility performed a multiple logistic

analysis using a model which included histories of salicylate ingestion, fever, headache, and sore throat. Adjusting for these potentially distorting variables, cases were found to be 11.5 ($p<0.001$) times more likely than controls to have taken salicylates. Similar results were obtained for each year of the study. The Ohio investigators also compared salicylate use in cases and controls matched by highest level of fever. Data had been collected on whether or not the case or control had a fever. If fever was present, the highest level of fever was recorded. The known fever levels were then divided into three strata (98.7 to 99.9; 100.0 to 101.9; 102.0 or higher). Although the prevalence of fever was significantly greater in cases than in controls (74 of 97 cases and 95 of 156 controls had fever ($p<0.01$)), among those with fever, at each temperature stratum salicylate use was consistently greater among cases (100 percent at each stratum used salicylate) than among controls (67 percent, 81 percent, and 75 percent used salicylate at the respective strata). A report of the Ohio study has been published in the August 13, 1982 issue of the *Journal of the American Medical Association* (Ref. 75).

Members of the FDA working group made a site visit to the Ohio Department of Health on March 8–10, 1982. They considered it important to evaluate the administration of medications and the development of symptoms on a daily basis to attempt to ensure that the administration of drugs before the onset of RS could be identified. By evaluating the data on a daily basis, the working group could attempt to adjust for any differences between cases and controls in symptoms that might be distorting the results of the analysis. By ascertaining which drugs had been administered before the onset of RS, the working group could test the hypothesis that the salicylate use by the cases might reflect treatment of the symptoms of RS rather than those of the antecedent illness and therefore would not be regarded as a possible cause of RS.

The only data which permitted such an evaluation were the data collected during the second year of the Ohio study. For that reason, the working group examined in detail the original State records of the 64 second-year cases and their associated controls. The working group transcribed the information concerning the daily administration of medication and the daily development of symptoms from the original State records. The working group also audited a sample of the first-year cases and the stage 0 cases that were not included in the study and the available information from all the fatal cases. On the basis of this evaluation, the working group concluded that the coding of information from the original investigational records had been performed with an unusually high degree of accuracy. No significant discrepancies were found by examining the original case and control questionnaire forms and comparing them with the coding of the data for computer compilation and analysis.

The Ohio second-year data enabled the FDA working group to analyze both the administration of medication and the development of symptoms on a daily basis, to attempt to adjust for confounding variables in cases and controls, and to attempt to ensure that the drugs under consideration were administered before RS was present. As was done with the Michigan data, FDA performed a multiple conditional logistic analysis of salicylate exposure during days 1 to 3 of the antecedent illness which adjusted for possible differences between cases and controls which might have been explained by differences in the presence of headache, fever, cough, and sore throat. These symptoms are those for which salicylate-containing products may have been used. One hypothesis would suggest that if the cases had different symptoms (e.g., more headache or fever) than controls, the higher salicylate user cases could be attributable to the presence of symptoms more likely to be treated with salicylates. In order to examine the possibility that salicylates might have been used to treat early symptoms of RS rather than an antecedent illness, cases (and their matched controls) with 4 or fewer days between the onset of the antecedent illness and the onset of RS were eliminated. On the basis of this analysis, FDA's working group found that cases of RS were still significantly more likely to have used salicylates. There was significantly less use of acetaminophen in the cases than in controls.

The FDA working group also considered a hypotheseis that some of the statistical association in the Ohio second year based on salicylate use during days 1 to 3 might be explained by the administration of salicylates after the symptoms of RS had already appeared in some of the cases. As noted earlier, RS typically develops in a child who appears to be recovering from antecedent illness. Approximately half of the cases (33) had at least a 1-day period between the symptoms of the antecedent illness and the onset of RS when no symptoms were recorded (these are referred to as biphasic cases). However, a number of cases (30) did not appear to have a symptom-free period between the recorded date of onset of the antecedent illness and the onset of RS (these are referred to as monophasic cases). In one case it was not possible to determine monophasic or biphasic status; therefore, that case was not used in the analysis.

Statistical analyses showed a different relative rate of salicylate usage between the monophasic cases and the biphasic cases as compared to their controls. Multivariate conditional logistic analysis of the data on the biphasic cases showed that these cases did not use salicylates in the first 3 days of their illness to any significantly greater extent than their controls. The same analysis of the group with the monophasic illnesses showed that these cases did have a significant excess of use of salicylates over their controls.

The FDA working group also compared salicylate usage in the biphasic versus the monophasic cases (Ref. 74). This analysis showed that fewer cases with biphasic illness used salicylates during days 1 to 3 than those with monophasic illness, although the difference is not significant (82 percent versus 93 percent, $p=.17$).

These analyses appear to indicate that there is a difference between the monophasic and biphasic cases. However, further examination of the data reveals that other factors require consideration in interpreting the relative rates of salicylate usage between cases and controls. The criteria upon which cases were divided into monophasic and biphasic groups were based solely on the symptom pattern reported in the cases. Consequently, the distribution of variables (e.g., salicylate use, headache, fever, etc.) in the controls for the two groups would be expected to be roughly the same. It is not the same. Salicylate use in the biphasic control group was significantly greater during days 1 to 3 than in the monophasic control group (76.5 percent versus 58.3 percent, $p<.05$). The FDA working group analyzed covariates (fever, headache, cough, sore throat) in the controls for the two groups and did not find symptom differences to explain the greater use of salicylates in the controls for the biphasic than for the monophasic patients.

The FDA working group recognized that at least three possible interpretations of these findings could be considered:

1. Because RS is thought to be a biphasic, rather than a monophasic illness, it might be argued that some of the monophasic cases either had no

antecedent viral illness, the viral illness was not detected, or the symptoms of the antecedent illness and the symptoms of RS were overlapping. Therefore, it could be further argued that in some of the monophasic cases, salicylates might not have been administered before the onset of RS, that salicylates might actually have been used to treat the symptoms of RS, and that salicylate use in those cases might not be implicated as a causative factor in the development of RS.

2. That salicylate use might hasten the development of RS.

3. That the division into groups with monophasic and biphasic illnesses might not have been meaningful and was associated with an artifactual difference in the respective control groups that resulted in irrelevant statistial differences in the relative risks calculated for the two groups of RS cases.

Because the FDA working group could not eliminate this third interpretation, it was unable to conclude that the statistical association in the Ohio second year could be explained by the administration of salicylates after the symptoms of RS had appeared.

4. *Working group summary.* The FDA working group considered that its analysis of the data from the second year of the Ohio study was pivotal to the assessment of the possible association between the use of salicylates in the preceding viral illness and the subsequent development of RS. The working group concluded that its analysis of the data from that study showed that patients with RS (cases) had a greater frequency of salicylate use during the first 3 days of the antecedent viral illness than did children matched for certain selected variables with an illness of a similar nature (controls). The working group found that cases of RS in the study were significantly more likely to have used salicylates, and this association continued even when the data were statistically adjusted to account for differences in cases and controls for the symptoms headache, fever, sore throat, and cough and when cases with 4 or fewer days between the onset of antecedent illness and the onset of RS were eliminated. In addition, the working group found there was significantly less use of acetaminophen in the cases than in the controls.

The FDA working group report also recognized that the association between salicylates and RS observed in the four State studies might be reflective of factors other than a causative role of salicylates in the development of RS. In addition, the report raised the question whether in some cases the symptoms of RS had developed earlier than was recognized, so that treatment was given after the onset of RS and not during the antecedent illness. Because the working group report reflected a preliminary review and was prepared to provide information for consideration at a public meeting, the working group did not resolve these questions before the public meeting.

D. *Reye syndrome workshop.* A Reye syndrome workshop sponsored by FDA, CDC, and the National Institute of Allergy and Infectious Diseases of the National Institutes of Health was held on May 24, 1982. A notice announcing the workshop was published in the **Federal Register** (47FR 20862; May 14, 1982) (Ref. 36). The workshop was scheduled to provide interested persons, including industry and consumer group representatives, an opportunity to discuss the currently available data on RS and to make written submissions and to give oral presentations. A transcript of the meeting was prepared (Ref. 37).

Before the workshop, FDA had made data available that was in its possession and on which it had relied in preparing the working group's preliminary review. The data in the agency's possession did not include the original forms used in conducting the four State studies. (The agency has since obtained the original data in the Ohio study (Ref. 111).) The data did include FDA's transcription of certain data from the second year of the Ohio study and the second year of the Michigan study (Ref. 38). In addition, the data included a data computer tape provided by the Ohio Department of Public Health on its RS investigation (Ref. 65).

The workshop was attended by invited experts from the academic community, the drug industry, and consumer organizations. The scientific panel members (primarily from the academic community) were asked to review and discuss the data and presentations, but were not asked to make formal recommendations to the sponsoring organizations. However, the members of the scientific panel were provided an opportunity to comment at the close of the meeting. Some of the panel members indicated that the available data were adequate to establish an association between salicylates and RS. Others indicated a belief that the data showed a possible association. Some members indicated that a causal relationship between salicylates and RS had not been shown. Several of the members agreed that physicians and the public should be advised of the possible risks of the use of salicylates to treat certain viral illnesses in children (Ref. 37).

E. *FDA evaluation of the four State studies.* FDA evaluated the four State studies to address questions concerning the design and execution of the studies. FDA's evaluation of the data from the four State studies included a careful consideration of questions raised concerning the quality of the data. Industry representatives and others contend that the data do not establish an association between salicylate use and the development of RS. In support of this contention they have raised objections to the design and execution of the studies generally, as well as objections to the evaluation of specific factors. FDA scientists have reviewed the questions raised thus far. Summaries of the questions, as well as the agency's tentative responses, follow.

1. It is claimed that the data from the State studies have not been adequately analyzed. Inadequacies in the data analysis, it is argued, included no independent review of the primary data base (e.g., completed questionnaires), no audit of the secondary data base (e.g., computer tapes coding information from the questionnaires), no proper multivariate analysis of the data, and no sensitivity analysis of the odds ratio that measured the purported salicylate-RS association. The argument is that because the data analysis was inadequate, the studies cannot be said to have demonstrated an association between salicylate use and RS.

As discussed above, the FDA working group did review the primary data from both Michigan studies and from both years of the Ohio study. The working group also performed a selected audit of the computer tapes from the Ohio study and concluded that the coding of information from the original investigational records had been done with an unusually high degree of accuracy.

The Ohio State Health Department performed a multivariate analysis of the data from the Ohio study and found a statistically significant association between RS and salicylate use. In addition, the FDA working group's analysis included multivariate analysis using the multiple conditional logistic model (Ref. 112). This form of analysis is primarily designed to analyze matched case-control data where adjustment for covariates is desired. The results of these analyses also support the conclusion that there is an association between salicylate use and RS.

The sensitivity analysis referred to in the criticisms of the State studies is intended to determine the effects of

misclassification on the odds ratio, the measure of association used in these studies. Theoretical studies in the literature (Refs. 40 to 45) have shown that if the misclassification bias is nondifferential, that is, the same level of misclassification exists in both the cases and controls, then the odds ratio tends towards the "null" hypothesis. In other words, the estimated odds ratio will always tend to be less than the true odds ratio. That is, if the same level of misclassification exists in both the cases and controls in the Reye's studies, then the cases are even more likely to have used salicylates in relation to the controls than the analyses have shown. However, if the misclassification is differential, affecting one group more than the other, then the estimated odds ratio can be either less than the true odds ratio or greater.

Without specific information as to the nature of any potential misclassification bias in these studies, the bias' effects cannot be estimated and, therefore, cannot be corrected for. In none of the studies reported are there data indicating that a differential misclassification is operating. Nor are there any supplementary data supporting such a claim. Therefore, a sensitivity analysis may be either unnecessary or impossible with respect to these RS studies.

2. It is claimed that the studies were conducted without a protocol that defined precisely the methods of data acquisition, data anlaysis, and study monitoring used in the studies. The suggestion is that lack of a protocol may lead to such problems as inconsistencies in interview techniques employed by different interviewers or inconsistent matching of cases and controls, which may distort the study results.

The FDA working group found that better documentation of operational procedures for the studies could have been provided. However, for both years of the Michigan study there was a protocol that included eligibility criteria, so that cases and controls could be consistently matched. Although there was no formal protocol for the Ohio study, the study did have an operational manual which described eligibility criteria, as well as the interviewing procedures. Thus, there were plans for both the Ohio and Michigan studies to guard against distorting inconsistencies.

3. It is claimed that there was no matching of cases and controls on the basis of severity of the antecedent illness. Thus, it is contended, the cases were sicker than controls with respect to such factors as the presence of fever, the degree of fever, and the amount of liquid intake during the acute illness. The severity of illness, it is argued, may have determined the parent's choice of antipyretic drug thereapy. The argument is that matching cases and controls for such variables as reduced fluid intake, use of antinauseant medication, and fever could eliminate the association between salicylate use and RS.

The investigators attempted to control for severity by matching cases with ill controls who were from the same classroom and who were ill at about the same time, as well as by matching as many variables as possible. Such matching included, for example, matching cases that had chickenpox with controls that had chickenpox and cases that had respiratory illness with controls that had respiratory illness. Matching with respect to the degree of fever was done in the second year in Michigan, but not in the other studies. In the second-year Michigan study, which included matching by temperature strata, 12 of 12 cases (100 percent) and 13 of 29 controls (45 percent) reported receiving salicylate-containing medications ($p < .002$). When highest-measured temperature was used restrospectively to match cases and controls in the statistical analysis of the first-year Michigan study, the difference in salicylate ingestion remained significant (100 percent of cases, 73 percent of controls ($p < .05$)). As discussed earlier, the Ohio investigators also restrospectively matched cases and controls by temperature strata. At each temperature stratum salicylate use was consistently greater among cases than controls. FDA's multivariate conditional logistic analyses, which adjusted for fever, showed that the association between salicylates and RS remains significant.

The data also indicate that the administration of antinauseants is not significantly associated with the antecedent illness, but may be associated with the symptoms of the onset of RS. This was confirmed by FDA's analysis of the second year of the Ohio study, which shows that most antinauseant use was on the day of onset of RS or later. With respect to reduced fluid intake, the question was asked in such a manner that data available with respect to this factor cannot establish whether the reduction in intake was associated with the antecedent illness or with the onset of RS. In addition, FDA's multivariate conditional logistic analyses adjusted for other indications of severity of illness, including cough, headache, and sore throat. After adjusting for these measures of severity of antecedent illness, the association between salicylates and RS remains significant.

4. It is claimed that interviewer bias influenced the results of the studies. Interviewer bias could have resulted form the fact that interviewers were not "blinded", i.e., they knew in advance that the parents they interviewed were the parents of cases rather than controls or of controls rather than cases. Such knowledge, it is argued, could cause interviewers to question one group of parents more closely than the other, thereby producing more, or more reliable, information from that group. Prior knowledge by interviewers that salicylate drugs were suspected more strongly than other factors of being asssociated with RS could also have biased the questioning. These forms of interviewer bias could have produced biased reporting by the interviewees. For example, if the parents of cases were more closely questioned than parents of controls, it is possible that they would have been more likely to recall the specific medications administered to their children. It is therefore possible that such parents would have been more likely to have remembered that they had administered aspirin, whereas parents of controls would have remembered only that they administered a fever-reducing drug of some sort, thus falsely increasing the incidence of aspirin use in cases compared with controls. It is also possible that if interviewers knew of a potential connection between salicylates and RS, they might have persisted in asking parents of cases about medications until receiving a response mentioning a salicylate product, whereas they might not have so persisted when questioning parents of controls.

Although it is true that interviewers knew in advance which families had cases and which had controls, precautions were taken to prevent the introduction of bias into the interviews by reason of such knowledge. Interviewers in the Michigan and Ohio studies received training designed to standardize interviewing technique, so that parents of cases and parents of controls would be asked the same questions in a similar manner.

FDA's review of the questionnaries used in the Michigan and Ohio studies revealed no basis for concluding that salicylate drugs had been given undue attention by the interviewers or that other forms of interviewer bias tainted the responses. Moreover, in the Arizona study and the first Michigan study and the first year of the Ohio study, those conducting the investigation had not concluded that salicylate drugs were more likely than other factors to be

associated with RS. The interviewers in those studies, therefore, were unlikely to have biased the results by any intentional or unintentional desire to elicit information concerning a hypothesis implicating salicylates in the development of RS. Furthermore, interviewers in the second year of the Ohio study were not informed by the investigators that a possible association between salicylate drugs and RS was suspected.

Finally, the absence of significant interviewer bias in the Michigan studies is suggested by the fact that similar numbers of drug preparations were reported by cases and controls. Because parents of cases and parents of controls reported almost the same numbers of drug preparations given, it does not appear that interviewers persisted longer in their questioning about medications with parents of cases than with parents of controls.

5. It is claimed that the Ohio study may have been flawed by a bias in case selection. A physician at one of the six clinical centers participating in that study has stated that some of the cases he reported to the Ohio State Health Department were excluded from the study (Ref. 78). He indicated that at least four of the cases he reported had no history of salicylate ingestion.

The FDA working group has reviewed the case selection in the Ohio study for each of the participating centers (Refs. 79 and 80). During the 2 years of the study, 11 RS cases were reported from the clinic with which this physician is associated. The Ohio Health Department excluded 5 of those 11 cases from the study for the following reasons: 2 cases were stage 0; 1 case was too young (about 1 year old); 2 cases could not be matched. These exclusions were consistent with the eligibility criteria established and with the procedures used during the period of this study. Of the 11 cases reported from this clinic 8 (73 percent) had used salicylates; of the 6 cases from this clinic which were included in the study, 4 (67 percent) has used salicylates.

The working group saw no indication that the case selection process pertaining to the cases reported from one center was unique. Of all the cases reported to the Ohio Health Department, 183 of 196 (93.4 percent) had used salicylates. Among nonsalicylate users who were not included in the 97 matched cases, 6 were stage 0, 2 were preschool, and 2 apparently could not be matched. There were 31 cases who were not matched, although they were eligible based on stage, degree of illness, and age. Of those, 29 (93.5 percent) had used salicylates. Thus, it does not appear that cases were selected for matching based on whether or not they had used salicylates.

6. It is claimed that product confusion among parents caused misclassification of the drugs used by cases and controls. Thus, it has been argued that some parents may have thought a salicylate product was used when, in fact, it was a nonsalicylate product. It is also asserted that the documentation confirming the medication histories is inadequate. The assumption is that because the parents of cases were usually interviewed in the hospital it would be less likely that the investigators confirmed the cases' medication histories by visually inspecting the medication bottles. Confirmation by inspecting the medication bottles of the controls would be more likely because the interviews were conducted at the parents' home.

In Ohio, there was an extensive effort to identify ingredients properly for single as well as combination drugs. In Michigan, the interviewer notified the family to prepare for the interview and to show the medication bottle to the interviewer. Although parents, in some instances, may have been confused as to the identity of the active ingredient, interviewers in both Ohio and Michigan usually obtained brand names of the drug administered, which were then checked to determine and record the active drug ingredient. In Ohio, 90 percent of the cases and 91 percent of the controls supplied brand names; 100 percent of the acetaminophen identification was by brand name.

It is true that the documentation does not show which product identifications were confirmed by visual inspection of the bottles and which were not. However, there is also no documentation showing that any of the visual confirmations revealed a contradiction between the brand name identified and the brand name on the bottle label. Thus, any effect of the visual confirmation on the study analysis remains conjectural.

7. Analyses have been submitted by industry representatives to show that there is no significant statistical association between salicylate use and RS if two subsets of the second-year Ohio cases identified by FDA's working group are examined (Ref. 101). The following subsets of the 64 second-year Ohio cases were analyzed: (1) The 48 cases with more than 4 days of symptoms before the onset of RS and (2) the 41 cases in which the relationship of salicylate use to onset of RS could be ascertained with reasonable certainty.

The working group's analysis of those 48 cases with more than 4 days of symptoms before the onset of RS showed a positive and statistically significant association between salicylate exposure and RS. The industry submission's analysis of those 48 cases showed a positive association that was, however, not statistically significant. The difference between the working group's finding and the industry submission's finding with respect to this subject appears to result from the differences in the databases of the two analyses. The industry submission's coding of subjects from the second year of the Ohio study for exposure to salicylates or nonexposure to salicylates differs from the working group's coding with respect to 11 subjects. This difference appears to be primarily due to the fact that the industry submission had coded controls as exposed if salicylates were used at any time during their illnesses, whereas cases were coded as exposed only if a salicylates were used early in the course of illness. The working group coded a subject as exposed only if salicylate was used during the first 3 days of the illness, and this same coding was applied to both cases and controls.

The working group coded exposure according to the first 3 days of illness only in order to determine whether the frequency of salicylate use was related to the severity of symptoms of the antecent illness. The first 3 days is the time period when symptoms of viral illnesses are likely to be most severe. The working group performed a multiple conditional logistic analysis to test whether differences in symptoms accounted for a greater frequency of salicylate use in cases and found that there was still a significant association of salicylate use with RS after accounting for these differences. The working group attempted both to assure that the database did not include salicylates that were being given specifically to treat Rs and to determine whether salicylate use was the result of more severe illness in cases than controls. The industry analysis did not compare equivalent time periods in cases and controls and did not adjust for the severity of illness when examining the relationship between salicylate use and RS.

The industry submission also analyzed a subset of 41 cases in which the relationship of salicylate use to onset of RS could be ascertained with reasonable certainty. The industry submission argued that with this subset of 41 there is also no statistically significant association between salicylate use and RS. FDA's working group had identified and studied this subset of 41 cases in order to determine

other salicylates were used for treatment of RS, regardless of whether they had been used initially for treatment of the antecedent illness. That is, the 23 cases that began salicylate use on day 1 or 2 of illness and continued until the onset of Rs were excluded from this subset because for those 23 cases it could not be determined when the salicylate use for the antecedent illness ended and the salicylate use for RS began. However, because this group of 41 cases does not include all RS cases who used salicylates before onset of RS, the association of RS with prior salicylate usage cannot be determined by comparing only these cases and their controls. Therefore, the industry submission's analysis using this subset of 41 cases to determine the frequency of use of aspirin before the onset of RS is an invalid approach.

8. The industry submission which analyzed the 48 and 41 case subsets also claimed that some of the product identifications recorded on the case report forms are insufficient to determine whether the products contained salicylates (Ref. 101). The industry submission argued that 7 of the subjects in the second year of the Ohio study (4 cases and 3 controls) who were identified as having been exposed to salicylate had received medications which had not been clearly identified as containing salicylates ("indeterminate" medications).

The submission argued that even when all 64 cases are examined, the assumptions about the 7 indeterminate medications lead to critical differences in the results. Using its database, the industry submission presented an analysis showing that when it is assumed that the 7 subjects who took indeterminate medications were exposed to salicylates, the result is a statistically significant association between salicylates and RS. However, when it is assumed that these 7 subjects were not exposed to salicylates, the association is no longer statistically significant. The submission argued that if only 3 of the indeterminant cases are assumed to be unexposed, the results are not statistically significant.

The industry submission based its identification of "indeterminate" medication on the fact that the trade names of some salicylate-containing products are very similar to the trade names of non-salicylate-containing products. For example, "Brand X" may contain aspirin and "Brand X-AF" may contain acetaminophen. FDA's working group assumed that a listing on a case report form for "Brand X" would mean literally that, and would not have been so listed if the brand name were at all different. Therefore, the working group listed these products as salicylates. However, if it were assumed (as the industry submission assumed) that the correct names of these products could not be determined, then the appropriate approach would be to exclude these subjects from the analysis. That is, if the salicylate exposure is unknown, that subject should not be included as either exposed or unexposed, because either assumption would improperly bias the results. When the subjects identified by the industry submission as having taken "indeterminate" medications are excluded from analysis of all 64 cases, the association between salicylate use and RS remains significant, regardless of whether the industry submission's database or the working group's database is used.

9. It is claimed that, even over relatively short periods of time, parents do not accurately remember significant details about medications they administered to their children, the symptoms their children had during illness, or their children's behavior patterns (e.g., fluid intake) during illness. If recall were equally inaccurate for both groups of parents, it would not ordinarily be expected to bias the information reported for cases and controls. However, in case-control studies parents of cases are typically interviewed shortly after their children's illness, whereas parents of controls are often interviewed weeks or months after illness, and this was true of the Ohio and Michigan studies. Also, parents of cases—children with RS—might remember important details concerning medication or severity of symptoms more clearly than parents of controls, whose children had a far less serious illness. Such differential recall, it is thought, could have biased the results of the Ohio and Michigan studies.

In both the Ohio and the Michigan studies the investigators attempted to identify and interview the parents of controls as quickly as possible, thus minimizing the time differential between the two groups of parents as much as is practicable in case-control studies. Nevertheless, neither the time diffeential, nor any possible difference in recall accuracy between parents of RS children and parents of control children, could have been entirely eliminated.

Two observations, however, tend to negate the existence of significant recall bias stemming from these factors. First, recall bias would not be expected to result in the selective underreporting of the use of salicylate drugs, and overreporting of the use of acetaminophen, by the control group parents. Recall bias should have produced, instead, underreporting of both medications by the parents of controls. The parents of controls would have had no reason to remember administering an salicylate product. Second, as previously noted, similar numbers of total drug products were reported by both cases and controls in the Michigan studies. Therefore, it does not appear that parents of controls had, in the time period between the child's illness and the interviewer's questioning, forgotten the medications they gave during the illness to any greater degree than the parents of cases had forgotten the medications they had administered.

10. It is claimed that the data do not establish a dose-response relationship between salicylate ingestion and the development of RS. It is argued that one would expect there to be such a relationship if salicylate drugs caused RS. The absence of such a relationship, it is argued, would suggest that a causal relationship between salicylate drugs and RS is biologically implausible.

It is correct that the data do not show a dose-response relationship between salicylates and RS. The data are inadequate to show either the existence or the absence of such a relationship. Demonstration of a dose-response relationship would clearly strengthen an association between salicylates and RS, but its absence does not negate the existence of an association. A correlation between salicylate blood levels and the development of RS has also not been clearly demonstrated. The methodologies reported often lack sensitivity and are affected by confounding factors, such as ketosis (which is present in dehydrated children, such as those who have RS). The significance of the blood levels measured depends on various factors, including information about the amount and timing of all salicylate drugs administered and the physical condition of the child. Data of the requisite quality to determine whether a dose-response relationship exists were not obtained during any of the studies.

Demonstration of a dose-response effect might strengthen the evidence of a causal relationship, but is not essential to show an association or a causal role of salicylates in RS. If the effect of salicylates in RS were dose dependent (e.g., the more toxin taken or present, the greater the toxic response), then such a relationship possibly could be demonstrated by clinical history and by laboratory tests. However, if the role of

salicylates is independent of dose, as it appears to be, then any exposure to salicylates, not necessarily exposure at toxic levels, could be a triggering factor in RS. That is, it is possible that a small amount of salicylates administered under certain circumstances will trigger RS and that it makes no difference whether or not larger amounts are administered. Thus, it is biologically plausible that salicylates could be a factor in causing RS even if no dose-response relationship were shown.

11. It has been argued that the association between salicylates and RS cannot be reconciled with certain facts concerning the identification and the patterns of incidence of RS. The argument is that because aspirin has been so widely used for so many years, it is unlikely that aspirin causes a disease that: (1) Has only recently been identified; (2) is very rare; (3) is geographically concentrated; and (4) occurs in Caucasians 90 percent of the time. It has also been argued that the facts that not all children who take salicylates for flu or chickenpox symptoms get RS and that some children get RS without having taken salicylates are inconsistent with a causal connection between salicylate use and RS.

The fact that RS was only identified as a specific disease in 1963 does not mean that it did not exist prior to that time—only that it had not yet been identified as a specific illness. RS is a rare disease; a rare disease is often not identified until sufficient information is accumulated and communicated to interested scientists to allow them to differentiate the symptoms of the disease from those of other diseases. That RS is rare does not, however, mean that there can be no causal relationship between salicylate use and RS. Administration of a drug can result in serious harm in only a small percentage of cases, yet nevertheless be the causal agent. For example, administration of chloramphenicol at a certain dosage has been estimated to cause fatal aplastic anemia in 1 out of 40,500 patients (Ref. 64). The data do show that not all children taking a salicylate for symptoms of flu or chickenpox develop RS. There must be more than one factor involved in the development of RS. That is, there may be certain preconditions, such as genetic predisposition, necessary before RS develops. Salicylate use could be one element in a chain of causes that lead to RS if most of the elements are present. Nor does the fact that a few cases of RS have been identified in which no salicylates were used prove that salicylates can have no causal role in RS. Salicylate use may be one among several possible causes, not all of which need be present for RS to develop. A number of environmental agents, such as insecticides, mycotoxins, and aflatoxins, have been suggested as possible factors in causing RS (Refs. 81 and 82). However, none of these agents have been confirmed as factors in causing RS by later studies.

Observed geographic differences in the incidence of Reye syndrome may reflect the varying levels of interest of health departments, communities, and physicians and the varying reporting requirements in different States. Whether some environmental agents present in different geographical locations may also be implicated in RS cases is unknown. As yet, there have been no adequate studies conducted to determine whether, in fact, RS does occur disproportionately in certain geographic areas. Even if future studies were to define geographic differences in the incidence of this disease, it is possible that factors other than salicylate use (including influenza and other as yet unidentified risk factors) might explain such observed differences.

Why 90 percent of the RS cases reported each year are among Caucasians is also not understood. It may be that Caucasians have different exposure to predisposing conditions of RS that have not as yet been identified. Perhaps there is a genetic predisposition to RS that is greater among Caucasians. As has been discussed before, salicylate use could be causally associated with RS without being the sole cause. Therefore, the fact that some factor other than salicylate use may result in more RS in Caucasians does not mean that salicylate use does not cause RS.

12. It has been argued that it is likely that a number of the children identified as cases did not actually have RS. The argument that some of the cases probably were misidentified rests on two main points: (1) Not all of the cases of RS were confirmed by liver biopsy and (2) there were low death rates among the study participants. It is claimed that the lack of biopsy confirmation is significant in light of an unpublished study conducted by Sokol, Heubi, and others in Cincinnati, OH. An abstract of their study indicates that 26 percent of subjects diagnosed as having stage IRS using CDC/NIH consensus conference diagnostic criteria were biopsy negative for RS (Ref. 83). It is also stated that in the second year of the Ohio study only 4 percent of the cases died, whereas the national death rate from RS is approximately 22 percent t. 40 percent.

It is true that not all of the RS cases were biopsy confirmed. The investigators in all four State studies used criteria developed by CDC (Ref. 1) and NIH (Ref. 46) to diagnose RS accurately. A liver biopsy is a procedure not to be undertaken lightly, especially in an uncooperative, critically ill child with defective coagulation (Ref. 46). Approximately 26 percent of the cases were biopsied in the 2 years of the Ohio study. None of the children included in the Ohio study who were biopsied were biopsy negative.

None of the patients in the Sokol-Heubi study were included in the four State studies (Ref. 84). All of the patients in the Sokol-Heubi study with stages II through V RS (four patients) were biopsy positive. Among the stage I RS patients, 14 of 19 were biopsy positive. Of these 14 biopsy-confirmed RS case, 100 percent had salicylate exposure; only 1 of the biopsy negative cases had salicylate exposure. Thus, although the Sokol-Heubi study suggests that there are difficulties in diagnosing stage I RS, the study also suggests that there is an association between salicylate exposure and biopsy-confirmed RS cases.

Mortality rates for RS cases have decreased since the 80 percent rate reported in Reye's original study (Ref. 4). In 1974 the death rate from RS in the United States was 41 percent (Ref. 77); in 1981 the national RS death rate was 28 percent (Ref. 1). It is likely that early recognition of RS and greater use of intensive medical support have resulted in the lowered mortality rate (Ref. 2). The RS death rate in Ohio in the last 10 years has been consistently lower than the national average—in Ohio the death rate was 23 percent in 1973, 13 percent in 1976, and 3 percent in 1977 (Ref. 56). A possible reason for the low Ohio death rates is that the children were identified as RS cases at a less severe stage and received prompt, aggressive supportive therapy. Although it is not entirely clear why the Ohio RS death rate has been consistently lower than the national average, the 4 percent death rate in the second year of the Ohio study is consistent with the usual low rate in Ohio.

Furthermore, as the American Academy of Pediatrics' Committee on Infectious Diseases has pointed out, if any misclassified cases could be eliminated from the analysis, it would be expected that an association between aspirin and RS would be strengthened rather than weakened (Ref. 47). This results from the fact that non-RS individuals, misclassified as RS

cases, would probably exhibit salicylate patterns more like their controls and hence would dilute an association. Thus, elimination of these cases would further enhance the differences in salicylate use between cases and controls, therefore strengthening an association.

13. It has been argued that an association between salicylates and RS cannot be reconciled with the fact that the liver pathology of RS is different from the liver pathology of salicylism and that the serum patterns of amino acids, free fatty acids, ketones, and urates in RS are different from the serum patterns of the same substances in salicylism.

The liver pathologies and the serum patterns of RS and salicylism do differ. It is generally agreed, however, that RS is neither the same as salicylism nor the results of salicylism. Therefore, it would not be expected that RS and salicylism would have the same liver pathologies and serum patterns. The fact that the liver pathologies and serum patterns of RS and salicylism differ would not negate the existence of an association between salicylism use and RS; it would also be irrelevant to the question of whether salicylism use might be a causal factor in the development of RS.

14. It has been argued that the association between salicylates and RS cannot be reconciled with the fact that the concentration of salicylates needed to produce one proposed mechanism for salicylates' role in RS occurs at levels that have probably not been reached in most cases. That is, it is claimed that the concentration of salicylates needed to produce a 50-percent inhibition of rate-limiting enzymes for mitochondrial oxidative phosphorylatin has not been shown to have been reached in most RS cases.

The mechanisms acting in the origin and development of RS are not fully understood. The possible mechanisms by which salicylates might contribute to causing RS are also not fully understood. One possible mechanism postulated for a causal role of salicylates in RS is that the salicylates inhibit certain mitochondrial functions. Whether this particular postulate can be supported theoretically or by future clinical data is not crucial in determining whether salicylate use plays a causal role in the development of RS.

15. It has been argued that the association between salicylates and RS cannot be reconciled with the fact that the incidence of RS in children with rheumatic disease (such as juvenile rheumatoid arthritis), who regularly receive high dosages of salicylates, is not higher that the incidence of RS in the general population.

The incidence of RS in children with rheumatic disease who are on high-dose salicylate therapy cannot be determined on the basis of the available data. Cases of RS among these children have been reported (Refs. 10 and 37 (at page 129)). More information on the incidence of RS in this group of children may be useful in understanding the relationship between salicylates and RS. It should be noted again that even if salicylate use is shown to be one causal factor in the development of RS, it is not the sole causal factor. The existence of an antecedent illness, such as the flu or chickenpox, has already been strongly implicated in the development of RS. Perhaps genetic predisposition is also a factor in what may be shown to be a chain of causal factors. Because children with rheumatoid arthritis already have a pathologic disorder, that disorder may be in some way associated with a greater or lesser likelihood of developing RS.

16. It has been argued that there is a medical risk in suggesting that salicylates not be used to treat high fever in children because of the possible harm, including convulsions and damage to the central nervous system, that prolonged high fever can cause. Suggestions have been made that consumers should not be subject to such a risk and that rather than warning consumers against salicylate use, the agency should advise consumers that they should exercise prudence in the use of all medications in children. It has been argued that cautioning against salicylate use will lead to more use of acetaminophen products, which pose risks of liver toxicity. It has also been suggested that a label warning on salicylates concerning RS might lead parents to believe that by not giving their children salicylate products they have removed all risk of RS.

A label warning statement being considered by the agency for certain salicylate-containing drug products would advise consumers against the use of salicylates in persons under 16 years of age with flu or chickenpox unless directed by a doctor. Fever is often associated with these diseases; prolonged high fever can lead to convulsions and, in very rare cases, permanent damage. There are, however, alternative antipyretic drugs that do not contain salicylates. Although there is a risk of liver toxicity associated with acetaminophen use, this risk stems from drug overdose and can be avoided in children largely through use of child-resistant containers. Salicylates also can be dangerous to children if taken in overdose.

More importantly, most levels of fever probably do not require any drug therapy and are not harmful. The American Academy of Pediatrics' Committee on Infectious Diseases has suggested that when a physician believes that control of fever is necessary, such alternative means of fever control as increased fluid intake and sponging with tepid water should be considered (Ref. 47). The labeling statement under consideration would not warn against salicylate use in children in all circumstances. The possible benefits of salicylates might outweigh the risk of Reye syndrome in certain patients, such as those with juvenile rhevmatoid arthritis for whom the risk of Reye syndrome may be less important than the benefits gained in treating this chronic debilitating disease.

Prudent use of all medications, including antipyretics in children, is, of course, advisable. However, such general advice may not be sufficient to protect against specifically recognized risks. The agency's educational campaign, discussed in detail below, informs parents about the symptoms of RS and stresses the importance of early emergency medical treatment. Because of the educational campaign parents should have increased awareness of the syndrome and be more likely to recognize it when it occurs. Warning parents through labeling statements about the possible risks of RS from treating certain childhood illnesses with salicylates would not necessarily imply that abstaining from salicylate use prevents RS.

17. It has been argued that, despite the uncertainties in the data, the public should be warned of the association between salicylate use and the development of RS. It is also claimed that, although the public should be advised generally to use caution in administering antipyretics to children, the available data do not justify a labeling warning requirement specifically for salicylate-containing products. In the June 1982 issue of *Pediatrics*, the American Academy of Pediatrics published a recommendation of its Committee on Infectious Diseases that "[i]nasmuch as salicylates are over-the-counter preparations, education of parents to their avoidance in influenza and varicella [chicken pox] requires a total community effort. We urge that the appropriate governmental agencies undertake appropriate review and necessary action to inform the public at large" (Ref. 47). On November 8, 1982, the Executive Board of the American

Academy of Pediatrics stated its belief that labeling aspirin-containing preparations as contraindicated in treatment of influenza or chicken pox "should be delayed until more conclusive evidence of the association of aspirin administration and Reye's Syndrome is shown by further investigation" (Ref. 85). Subsequently, on November 19, 1982, the American Academy of Pediatrics stated that it "continues to be concerned about the possible association of aspirin and Reye's Syndrome and has alerted physicians to use caution in recommending aspirin for treatment of influenza and chicken pox symptoms" (Ref. 86). The American Academy of Pediatrics added that it believed "the current labeling [on aspirin] which includes 'flu' among those conditions which may be treated with aspirin is inappropriate" and recommended deletion of the flu indication from the labeling of children's aspirin-containing products (Ref. 86). These and other comments raise questions about the quality of data which should exist to support regulatory actions. The comments also raise questions about the differences between two types of agency actions—advice to the public and label warning requirements. These questions are discussed in the following section.

F. *Regulatory evaluation.* The agency has statutory authority to undertake various kinds of activities to protect the public health, including initiating public educational campaigns and requiring labeling warnings on drug products. FDA has evaluated the recent reports on the relationship between salicylate use and RS and has considered the potential risks to the public health suggested by those reports in considering which related activities to initiate.

Section 310(b) of the Public Health Service Act, 42 U.S.C. 242o(b), directs the Secretary of HHS to issue "information related to public health, in the form of publications or otherwise, for the use of the public" and to publish "other pertinent health information for the use of persons and institutions concerned with health services." Section 311(a) of the Public Health Service Act, 42 U.S.C. 243(a), directs the Secretary to "advise the several States on matters relating to the preservation and improvement of the public health." Functions of the Secretary under these sections that relate to the responsibilities of FDA have been delegated to the Commissioner of Food and Drugs. See 21 CFR 5.10 (a)(2), (19).

Section 705(b) of the Federal Food, Drug, and Cosmetic Act, 21 U.S.C. 375(b), authorizes the Secretary to disseminate information regarding drugs "in situations involving, in the opinion of the Secretary, imminent danger to health or gross deception of the consumer." The magnitude of the potential danger need not be estimated, however, because section 705(b) is not a limitation upon the authority of the Secretary. It has been held that "even in the absence of this statute there would be nothing to prevent the [Federal officials] from disseminating information to the public. The [Federal officals] are performing a public duty when they are urging the use of certain treatments or warning the public against the use of certain treatments." *Hoxsey Cancer Clinic* v. *Folsom*, 155 F. Supp. 376, 378 (D.D.C. 1957). See *United States* v. *An Article of Device . . . Dispulse Mfg. Corp.*, 262 F. Supp. 728 (D. Conn. 1967). The functions of the Secretary under the Federal Food, Drug, and Cosmetic Act have also been delegate to the Commissioner of Food and Drugs. See 21 CFR 5.10(a)(1).

As discussed above, several groups and numerous individuals have suggested that, until the relationship between salicylate use and RS is clarified, physicians and the public should be advised of the possible risks of using salicylates to treat certain viral illnesses in children. Case-control studies are inherently limited by possible distortions resulting from interviewer bias, recall bias, or imperfect matching of cases and controls. However, the data which first indicate potential health risks are often flawed or equivocal. In some cases, it may be years before data are available to establish definitively that a serious health risk accompanies the use of a particular product.

With rare diseases, such as RS, the agency has no option except to rely on case-control studies, because prospective studes of a population at risk for a disease that may occur, as here, at an annual rate of less than 5 cases per 100,0900 population under 16 years of age would require an enormous number of subjects. The four State studes are consistent in their results. Collectively, the result of the studies on their face would appear to establish an association between salicylate ingestion and RS—nearly every child who developed RS had take salicylates (137 of 141); while far fewer of the control group (151 of 247) had taken salicylates. Moreover, the Ohio and Michigan studies appear to establsh a reverse association with the administration of acetaminophen (a nonsalicylate antipyretic and analgesic), in that control subjects were much more likely to have received this drug than were the cases.

A statistical association as reported by the four State studies might reflect a causative role for salicylates in the development of RS, or it might be associated with other factors. Although RS is a rare disease, the mortality rate is high. Until the relationship between salicylates and RS has been clarified, FDA believes that the interests of the public health require that physicians and the public be advised of the possible risks of administering salicylate-containing medication to children with flu or chickenpox. This position is consistent with the views expressed in a recent editorial in the August 13, 1982 edition of the *Journal of the American Medical Association* (Ref. 76).

On June 4, 1982, the Secretary of Health and Human Services announced that "medical experts have concluded that the use of salicylates such as aspirin in children with influenza and chickenpox and certain other viral infections has been sufficiently associated with Reye Syndrome to warrant warning physicians and parents" (Ref. 48). The Secretary announced that he had directed FDA to undertake an educational campaign aimed at medical care personnel, pharmacists, and parents. In addition, the Secretary directed the Surgeon General of the U.S. Public Health Service to issue an advisory. On September 20, 1982, the Secretary announced the details of the educational campaign that had been undertaken. These initiatives are explained in detail below.

As discussed in detail above, the four State studies reporting an association between salicylate use and RS have been extensively criticized. In addition to comments pointing out the inherent limitations of case-control studies, specific questions about the design, execution, and analyses of these particular studies have been raised. Certain individuals, as well as the Executive Board of the American Academy of Pediatrics, have maintained that a labeling warning statement concerning salicylate use and RS would be premature at this time. On November 18, 1982, the Department of Health and Human Services announced that the American Academy of Pediatrics Executive Board's statement of November 8, 1982 (Ref. 85) is the first time that concerns have been raised by an independent scientific body and that it is critical that they be resolved. The announcement advised that the Secretary has decided that new

government-supported studies are necessary to help resolve the scientific dispute over the reported association between RS and salicylate-containing drugs. The announcement also advised that the Secretary has directed the Public Health Service to make recommendations to him for new research to help resolve the scientific dispute. (A protocol for a new study had been submitted earlier by industry representatives (Ref. 87)). The announcement pointed out, however, that a significant body of qualified opinion believes that the available scientific evidence sufficiently establishes an association that the public should be informed. Accordingly, the announcement advised that the Secretary has decided to continue the previously initiated public educational campaign to warn parents and professionals of the need for caution. The continuation of the public educational campaign is consistent with the statement of the American Academy of Pediatrics that was issued on November 19, 1982 (Ref. 86).

Recognizing the controversy over whether the results of the four State studies justify requiring label warnings at this time, the Secretary on November 18, 1982, also announced that this advance notice would set forth the available information and invite comments on whether label warnings should be required. Evidence of a potential public health risk may be sufficient to make public education appropriate but may not necesarily justify requiring revised product labeling.

Any proposed rule concerning an RS-salicylate labeling warning would be promulgated under the authority of sections 201(n), 502 (a) and (f), and 701(a) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 321(n), 352 (a) and (f), and 371(a)). If warranted by new scientific information or by the response to this advance notice, the possible labeling warnings announced in this notice may be required through an interim final rule (i.e., one with immediate effect). The possible label warnings and other labeling revisions under consideration are discussed in detail below.

II. Educational Activities

A. *Departmental initiatives*—1. *Surgeon General's advisory.* The Surgeon General of the U.S. Public Health Service issued a Surgeon General's advisory in the *Morbidity and Mortality Weekly Report* of June 11, 1982 (Ref. 49). That advisory recommended against the use of salicylates and salicylate-containing medications for children with influenza and chickenpox. The association of salicylates with RS, the Surgeon General states, "is based upon evidence from epidemiologic studies that are sufficiently strong to justify this warning to parents and health care personnel."

2. *FDA Drug Bulletin.* FDA issued an article in the August 1982 *FDA Drug Bulletin* which was distributed to over one million health care professionals, including physicians, pharmacists, and nurses (Ref. 88). The article reviews the data generally and advises caution in the use of salicylates in those viral illnesses particularly associated with the development of RS.

3. *FDA Consumer.* FDA also included an article on RS in the October issue of its publication, *FDA Consumer* (Ref. 89). This article reviewed the information on RS in terms understandable to the lay public and pointed out that aspirin and other salicylates may be associated with RS. Reprints of the article were sent to all consumer affairs offices of FDA for distribution to the public.

4. *Surgeon General's newspaper column.* The Surgeon General issued a newspaper column that discussed the suspected relationship between aspirin and RS and advised against giving aspirin to children with chicken pox, influenza, or a flu-like illness (Ref. 90). Approximately 8,000 copies of the newspaper column were distributed in early October.

5. *Radio public service announcements.* The Surgeon General also made recordings explaining that there may be an association between Reyes syndrome and aspirin and cautioning parents not to give aspirin when their children have flu or chickenpox (Ref. 91). Approximately 8,000 copies of these radio announcements were sent to radio stations on October 8, 1982.

6. *Question-and-answer brochures.* An RS information brochure in question-and-answer format has been made available on request to pharmacies and primary care physicians (Ref. 92). Approximately 673,000 copies of the brochure have been supplied for distribution.

7. *Dear Consumer letter.* A "Dear Consumer" letter offering copies of the question-and-answer brochure was mailed October 8, 1982, to approximately 13,000 consumers (Ref. 93).

8. FDA continues to work with health professional groups, including physicians (particularly pediatricians), and all other related organizations to transmit relevant information.

9. FDA continues to work with consumer and other organizations to transmit relevant information.

B. *Other informational activities.* A number of other publications disseminated information concerning the relationship between salicylates and RS. For example, the *Journal of the American Medical Association* of June 11, 1982, included a report of the Michigan study in a paper entitled, "Aspirin as a Risk Factor in Reye's Syndrome" (Ref. 35). The June 1982 issue of *Pediatrics* included a special report on "Aspirin and Reyes Syndrome" which included the recommendation of its Committee on Infectious Diseases of the American Academy of Pediatrics that "aspirin should not be prescribed under usual circumstances for children with varicella [chickenpox] or those suspected of having influenza on the basis of clinical or epidemiologic evidence" (Ref. 47). The recommendation also urged that appropriate governmental agencies undertake appropriate review and necessary action to inform the public at large.

In addition to Federal governmental efforts, a number of State health agencies have taken action to publicize the association between salicylates and RS. For example, the report of the Michigan studies notes that the possible association between aspirin and RS had received extensive publicity in Michigan.

III. Possible Labeling Requirements Under Consideration

Having reviewed the four State studies in light of the questions concerning the studies recognized by its own staff as well as the questions raised by industry representatives, consumer representatives, and health professionals, FDA is considering proposing a rule that would require the labeling of certain OTC and prescription salicylate-containing products to bear a warning against use in persons under 16 with flu or chickenpox. In order to assist the agency in determining whether to propose an RS-salicylate warning, FDA is in this advance notice requesting comments on the available data—e.g., on the design, execution, and analysis of the relevant studies and on the quality and strength of any demonstrated RS-salicylate association. FDA has suggested above some possible responses to questions concerning the studies that have already been raised; comments on these tentative responses are also invited.

On September 20, 1982, the Secretary announced the texts of warning

statements that the agency is considering proposing to be required on the labeling of salicylate-containing products. For over-the-counter (OTC) drugs, a proposed warning might read: "Warning: This product contains a salicylate. Do not use in persons under 16 years of age with flu or chicken pox unless directed by your doctor. The use of salicylates to treat these conditions has been reported to be associated with a rare but serious childhood disease called Reyes syndrome." The agency believes that the term "flu" is commonly understood to include influenza and a variety of other viral illnesses. Thus, flu and chicken pox would cover the viral illnesses that have been associated with RS. For prescription drugs, a proposed warning might read: "Drugs of this class, salicylates, have been reported to be associated with the development of Reyes syndrome in children under 16 years of age with chicken pox, influenza, and influenza-like infections." In addition to comments concerning the data on the relationship between salicylates and RS, the agency invites comments on the specific working of any RS warnings that might be proposed for salicylate-containing products.

The agency also invites comments on the appropriate scope of any proposed RS warnings for salicylate-containing products. FDA is considering proposing that RS warning statements appear in the labeling of all systemically absorbed salicylate-containing prescription drugs for human use that are administered orally, rectally, or parenterally and of all systemically absorbed salicylate-containing OTC drugs for human use that are administered orally or rectally. The salicylate in the product may be present either as a single ingredient or in combination with one or more other ingredients. Thus, a proposed rule would apply not only to products that contain aspirin, but also to drug products that contain other salicylates, such as aminosalicylic acid, sodium salicylate, sodium aminosalicylate, magnesium salicylate, choline salicylate, bismuth subsalicylate, aluminum aspirin, and calcium carbaspirin. Salicylate-containing drug products that would not be included would be those that are administered topically, and those that are used as mouthwashes.

Salicylate-containing drug products are probably the most widely used OTC drug products on the market. Salicylates are commonly used in analgesic drug products for the temporary relief of occasional minor aches, pains and headache and in antipyretic products for the reduction of fever. Salicylates are also often combined with OTC cold, cough, and allergy drug products for their analgesic and antipyretic effect. Although these classes of products constitute the largest use of salicylates, salicylates are also used in other categories of drug products, such as antidiarrheals.

Salicylates are usually used in prescription drug products in combination with other active ingredients, although some salicylates, such as aminosalicylic acid, may be used as a single active ingredient. Many prescription drug products containing a salicylate, either because of the other active ingredients with which they are combined or because of the specific indication of a particular salicylate, would not be used in children or adolescents under 16 years of age to treat flu or chickenpox. For example, the indications for products containing aminosalicylic acid or sodium aminosalicylate are for use as an antitubercular product. It is possible, however, that such a product could be administered to an individual under 16 years of age during the flu season, and that this might put that individual at risk. And there are other prescription combination salicylate-containing products that, though not administered for treating flu or chickenpox, could also be administered during the flu season to a child or adolescent. For this reason, the agency is considering proposing a rule that would require that all systemically absorbed salicylate-containing prescription drug products for human use administered orally, rectally, or parenterally carry an appropriate warning in their labeling.

The location of an RS warning statement on OTC drug product labeling is another issue on which the agency invites comment. The agency is considering proposing that all OTC drug products subject to the rule bear the required warning statement on all accompanying labeling, such as the outside container or wrapper label, and on the package insert. If the immediate container label contains warnings, that label would also be required to bear the required warning statement. The warning statement would be required to appear as the first warning under the heading "Warning" on all labels and labeling on which it would be required to appear. The agency is also considering proposing that, for prescription drug products subject to the proposed rule, the warning be required to appear in the "Warnings" section of the prescription drug labeling described in § 201.100(d) (21 CFR 201.100(d)).

The agency also in contemplating proposing to amend § 201.314 to require that the labeling for OTC and prescription salicylate-containing drug products subject to the proposed rule packaged only for use in children (pediatric products) not be permitted to recommend the product for us in flu or chickenpox.

The labeling of OTC salicylate-containing drug products subject to the proposed rule under consideration and packaged only for use in adults or that include directions for use in both children and adults would be permitted to continue to include a recommendation that the product be used for the symptomatic relief of flu or chickenpox. Because an adult product could be used in adolescents under 16 years of age, however, any recommendation for use in flu or chickenpox would be required to be followed immediately by the statement, "See salicylate warning."

Recognizing that not all consumers read the warnings contained in the labeling of OTC drugs that they have purchased frequently, the agency might propose to require a statement to be added to the "Directions" section on the immediate container label of OTC drug products, if such label bears such information, and in the "Directions" section of all accompanying labeling. The "Directions" section of the labeling is the section that includes information on how much of the product to take and how often to take it. This section is probably the most widely read section of OTC labeling. The statement that might be proposed to be required in the "Directions" section is as follows: "For persons under 16 years of age see warning against use of salicylate for flu or chickenpox." The agency invites comments on this approach or on alternative ways to bring this information to the attention of the consumer.

The agency also requests information on how rapidly industry would be able to comply with a labeling warning requirement for salicylate-containing OTC and prescription products. FDA believes that it could be feasible to require revised labeling to appear on salicylate-containing products within 90 days of the date a final rule was published in the **Federal Register**. The agency is considering proposing that any product subject to the rule that does not bear the required labeling statements and that is initially introduced or initially delivered for introdution into interstate commerce 90 days after publication of the final rule would be considered misbranded and, therefore, subject to regulatory action.

FDA is not now contemplating an immediate market withdrawal of all salicylate-containing products upon the effective date of a final rule. A requirement for the labeling of all salicylate-containing drug products already shipped in interstate commerce that would take effect soon after a final regulation was published would be impracticable and extremely difficult to monitor or enforce. Most salicylate-containing products subject to the proposed rule under consideration are OTC products, with aspirin-containing products being the most widely sold and available. Aspirin, as well as many other OTC salicylate-containing products, are available not only in pharmacies, but in various types of other retail outlets, including grocery and convenience stores.

FDA does not now possess sufficient information about the effects that market withdrawal of salicylate-containing products would have on the supply of needed medications to suggest a suitable exemption period. The agency invites comment on an appropriate period of time to allow for exhaustion of supplies of salicylate-containing products initially introduced or initially delivered for introduction into interstate commerce before the effective date of a final rule.

IV. Economic and Environmental Impact

FDA has preliminarily examined the Regulatory Impact and Regulatory Flexibility implications of the proposed regulation under consideration in accordance with Executive Order 12291 and the Regulatory Flexibility Act. The agency estimates that a proposal like that being considered would impose direct one-time costs totaling approximately $15–17 million, of which $12–$13 million corresponds to direct expenses of label modifications to be accomplished within a relatively short compliance period. The other one-time costs would be for possible product reformulations and/or new product marketing expenses. The agency also estimates indirect effects on consumer expenditures as a result of shifts of purchases from aspirin-containing to higher prices acetaminophen-containing products in response to label warnings. This expenditure increment would be estimated initially at $40–$60 million per year but would be expected to decline as product proliferation increases price competition in markets for acetaminophen products. These impacts taken together are below the thresholds for a major rule as defined in Executive Order 12291.

The impacts on small business are also believed to be insufficient to warrant a Regulatory Flexibility Analysis. Most of the direct relabeling costs would be expected to be incurred by the larger firms that dominate total sales of affected products. Impacts on small firms of sales shifts from aspirin-containing to acetaminophen-containing would not be expected to be significant because data in the Census of Manufacturers strongly suggest that only a few small firms sell solely or largely aspirin-containing products. The agency requests that interested persons submit any information that would aid FDA in assessing the economic impact of a proposed rule on salicylate-containing product labeling.

The agency also believes that the action under consideration is of a type that would not individually or cumulatively have a significant impact on the human environment. FDA invites comments on any potential environmental consequences of the action discussed in this advance notice of proposed rulemaking.

List of Subjects in 21 CFR Part 201

Drugs, Labeling.

V. References

The following information has been placed in the Dockets Management Branch (address above) and may be seen by interested persons from 9 a.m. to 4 p.m., Monday through Friday.

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89. Food and Drug Administration, "Reye Syndrome Spells Caution to Parents", *FDA Consumer,* 16: 19–21, October, 1982.

90. Koop, C. E., "Caution the Best Policy in Use of Aspirin with Children", for use by newspapers, undated.

91. Letter from Dr. Koop to Public Service Director dated October 8, 1982 enclosing a public service announcement.

92. Letter from Dr. Brandt to Dear Colleague dated October 8, 1982 enclosing a brochure entitled Reye Syndrome.

93. Letter from Mr. Grant to Dear Consumer dated October 8, 1982 concerning Reye Syndrome.

94. Bellman, M. H., E. M. Ross, and D. L. Miller, "Reyes Syndrome in Children under Three Years Old." *Archives of Disease in Childhood*, 57: 259–263, 1982.

95. Andresen, B. D., et al., "Aspirin and Reyes Disease: A Reinterpretation", *The Lancet*, pp. 903–904, April 17, 1982.

96. Check, W. A., "Reye's Syndrome-Aspirin Link a Bit Stronger", *Journal American Medical Association*, 247: 1534–1535, March 19, 1982.

97. Rodgers, G. C., "Salicylate and Reye's Syndrome", *The Lancet*, p. 616, March 13, 1982.

98. Memorandum of Plough, Inc., and Sterling Drug Inc., "Reye Syndrome and Salicylates", dated June 22, 1982, 34 pages.

99. Letter from Stanley Temko to Juan del Real dated June 28, 1982 enclosing one newspaper article and four journal articles that are of interest in connection with review of Reye Syndrome.

100. Letter from Dr. White to Secretary Schweiker dated November 24, 1982 offering assistance and cooperation in designing a study on Reye Syndrome.

101. Biometric Research Institute, Inc., report of Phase I "Review of the Ohio Department of Health Case—Control Study of Reye's Syndrome", prepared for Glenbrook Laboratories, Inc., and Schering-Plough Corporation dated August 20, 1982.

102. Memorandum from Dr. William Jordan to Influenza Program Officer dated July 26, 1982 concerning "Reye Syndrome in Japan".

103. Memorandum from Dr. Thomas Hayes to Mr. Paul Fehnel dated November 24, 1982 concerning "BRI Review of Report on Reye's Syndrome".

104. Letter from Bruce Gelb to Secretary Schweiker dated September 7, 1982 and response dated November 18, 1982.

105. HHS press release on Reye Syndrome dated November 18, 1982.

106. Memorandum from Dr. Eileen Barker to Paul Fehnel dated November 23, 1982 concerning "BRI Report and Agency Response".

107. Memorandum from Division of Biometrics to Stanley Edlavitch dated November 22, 1982, concerning "Analysis of the Reye Syndrome Data Used in the Phase I Report by Biometrics Research Institute, Inc."

108. FDA Talk Paper on "Reye Syndrome and Aspirin Update" dted November 16, 1982.

109. Memorandum from Stanley Edlavitch to Paul Fehnel dated November 23, 1982 concerning "Materials for Advance Notice of Proposed Rulemaking".

110. Committee on the Care of Children, press release dated November 16, 1982.

111. Case report forms from 2-year Ohio Study.

112. Computer printouts of FDA working group's multiple conditional logistic analyses of data from second year of 2-year Ohio Study.

Interested persons may, on or before February 28, 1983 submit to the Dockets Management Branch (address above) written comments regarding this advance notice of proposed rulemaking. Two copies of any comments are to be submitted except that individuals may submit one copy. Comments are to be identified with the docket number found in brackets in the heading of this document. Received comments may be seen in the office above between 9 a.m. and 4 p.m., Monday through Friday.

Arthur Hull Hayes, Jr.,

Commissioner of Food and Drugs.

Richard S. Schweiker,

Secretary of Health and Human Services.

Dated: December 20, 1982.

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