



revised 10-day and 5-day warnings for analgesic drug products in § 343.50(c)(1)(i), (2)(i), and (3) in this tentative final monograph adequate to warn consumers to obtain professional help if symptoms persist or get worse or if new symptoms occur.

22. Two comments objected to the 5-day limitation of use of analgesic and antipyretic drug products by children under 12 years of age in the Panel's recommended warning statement in § 343.50(c)(1)(ii). The comments agreed with the Panel that the period of OTC use of analgesic and antipyretic drugs in children under 12 years of age should be limited, but disagreed over the length of time. Suggested alternatives were 2 or 3 days. One comment argued that this warning implies that OTC analgesic drug products are unsafe or toxic if used longer than 5 days.

The agency is proposing the following revised warning for children 2 years to under 12 years of age in § 343.50(c)(2)(i): "Do not give this product for pain for more than 5 days or for fever for more than 3 days unless directed by a doctor. If pain or fever persists or gets worse, if new symptoms occur, or if redness or swelling is present, consult a doctor because these could be signs of a serious condition," (see comment 18 above).

The comments submitted no data to support their suggestions for shorter time limitations. The Internal Analgesic Panel based its recommendation of a 5-day limitation for children on reports from poison control center data and on computer simulations that demonstrated that the plasma salicylate level could exceed 20 milligrams per 100 milliliters (mg/mL) (a toxic level) "among some smaller children of a particular age category following the recommended dosage schedule after 5 days" (42 FR 35368). The agency believes these data provide sufficient reason to propose the Panel's recommended 5-day use limitation for children.

23. Several comments opposed the number and length of warning statements the Panel recommended for OTC analgesic and antipyretic drug products. One comment expressed concern that an extensive list of warnings for products containing aspirin, compared to a shorter list for acetaminophen drug products, will lead consumers to conclude that aspirin drug products are more toxic and less useful than acetaminophen drug products. Other comments urged FDA to limit warning statements to those that are scientifically documented, clinically significant, and important to the appropriate use of the products by the average consumer. These comments

further urged that the statements be combined and condensed for ease of consumer understanding and to avoid label clutter that may cause consumers to ignore cautions and warnings in the labeling. One comment suggested the use of supplementary circulars, etc.

FDA agrees that the warning statements for OTC drug products should be limited to those that are scientifically documented, clinically significant, and important for the safe and effective use of the products by consumers. The agency is requiring warning statements for each ingredient on this basis, not on the basis of a comparable number of warnings for each ingredient. Warning statements are also being combined and condensed whenever possible for ease of consumer understanding. In addition, manufacturers are free to design ways of incorporating all required information in labeling, e.g., using flap labels, redesigning packages, or using a package insert.

24. Many comments opposed warnings that cite organs of the body as possible sites of damage by internal analgesic drug products, with some comments referring specifically to the Panel's recommended liver warning for acetaminophen in § 343.50(c)(5)(i). These comments argued that naming an organ that may be injured from an acute overdose or from excessive use of an analgesic drug would place the responsibility of recognizing organ damage on the consumer, who would then be assuming the role of a physician. The comments further argued that this kind of label warning may be misunderstood and may either alarm or cause anxiety in consumers who use drugs rationally. On the other hand, the comments added, such labeling may provide information that may induce individuals to harm themselves.

The comments favored a single, more general warning for all OTC internal analgesic drug products, such as the following: "Do not take this product for more than 10 days unless directed by a physician. Excessive use over a long period of time may cause permanent injury." One comment suggested that, if such a general warning is not adopted, all OTC drug products should bear labeling which fully discloses the conditions under which damage may occur.

The agency is not proposing to include the general warning suggested by the comments in this tentative final monograph. FDA believes that the self-medicating consumer should be made aware of potential risks of a particular OTC drug product through label warnings. As discussed in comment 25

below, the agency agrees that the warnings need not specify the toxic effects on particular organs of the body that can be caused by acute overdose of a drug, as in a suicide attempt, and is not proposing the Panel's recommended liver warning for acetaminophen in this tentative final monograph. However, the agency concludes that the warnings should include specific information on the known side effects or adverse reactions that may occur from use of the drug according to labeled directions, as well as potential dangers that may occur if the labeled directions are exceeded.

The agency concludes that when medical evidence shows that toxicity is associated with the use of an OTC drug, either within its recommended dosage or when used beyond its recommended time limit or dosage (except for acute overdose), it is appropriate to warn consumers of the potential toxicity. In such cases it may be necessary to include organ-specific warnings as well as general labeling statements.

25. Many comments opposed the liver warning recommended by the Panel for acetaminophen drug products in § 343.50(c)(5)(i). "Do not exceed recommended dosage because severe liver damage may occur." Some comments argued that acetaminophen taken in recommended OTC dosage ranges shows no evidence of hepatotoxicity and that the labeling required in § 330.1(g), "Keep this and all drugs out of the reach of children. In case of accidental overdose, seek professional assistance or contact a poison control center immediately," provides sufficient warning to consumers. The comments expressed concern that the liver warning recommended by the Panel may discourage consumers from ever using acetaminophen and that this warning may also encourage suicidal persons to abuse acetaminophen drug products. The comments also argued that the liver warning is especially inappropriate for children's acetaminophen drug products because there is a lack of documented fatalities and serious liver damage in children from acute acetaminophen overdose. The comments stated there may be differences between the metabolism and pharmacokinetics of acetaminophen in children and adults that would cause children to be less vulnerable to acetaminophen toxicity.

Other comments endorsed the recommended liver warning and pointed out that there are no unique signs of acetaminophen toxicity, such as ringing in the ears (tinnitus), and that symptoms of acetaminophen toxicity do not appear until a few days after the overdose.

Noting that consumers are increasing their use of acetaminophen and that fatalities and liver damage have occurred in children, the comments argued that the recommended warning may discourage consumers from exceeding the recommended daily OTC dosage of acetaminophen and make consumers and doctors aware of the consequence of acetaminophen overdose. One comment, concerned about toxicity from the chronic use of acetaminophen in dosages of less than 4 grams (g) per day, suggested that the proposed liver warning be revised to place additional emphasis on the recommended limit of self-treatment with acetaminophen as follows: "Do not exceed recommended dosage or take for more than 10 days, because severe liver damage may occur." Another comment suggested that the recommended warning be revised to state the dosage that will cause hepatotoxicity, for example, 40 or more 325-mg tablets taken as a single dose.

After evaluating the data and information submitted, the agency has tentatively decided not to adopt the liver warning recommended by the Panel in § 343.50(c)(5)(i). The agency is aware that liver damage can occur from acetaminophen overdose, as explained by the Panel (42 FR 35414). However, the agency believes that warnings need not include information on the specific toxic effects on organs of the body caused by acute overdose of a drug, as in suicide. (See comment 24 above.) The agency also considers it inadvisable to specify hepatotoxic dosage levels in consumer labeling, as one comment suggested, because such labeling could be suggestive to suicidal individuals.

The agency has noted two reports of hepatotoxicity in children who overdosed on acetaminophen. Arena, Rourk, and Sibrack (Ref. 1) described a 3-year-old girl who ingested 35 tablets of acetaminophen 325 mg and suffered decreased consciousness, vomiting, and enlargement of the liver and spleen. At that time the serum ammonia level was 82 micrograms per deciliter ( $\mu\text{g}/\text{dL}$ ). She was admitted to the hospital about 24 hours after ingestion. The serum acetaminophen level was 94 micrograms per milliliter ( $\mu\text{g}/\text{mL}$ ) 24 hours after ingestion; 48 hours after ingestion it dropped to 26  $\mu\text{g}/\text{mL}$ . Seventy-two hours after the overdose, serum transaminase (liver enzyme) levels revealed a peak serum glutamic-oxaloacetic transaminase of 20,376 International Units (I.U.) and a peak serum glutamic-pyruvic transaminase of 13,303 I.U. The patient was alert and in

good spirits by the second day in the hospital and was discharged 1 week later. Seven weeks after discharge her liver enzymes were normal.

Although this child weighed only 31 pounds and had ingested 11.375 g acetaminophen, resulting in phenomenal transaminase levels and a high plasma level of acetaminophen at 24 hours, she survived without any aftereffects. As one comment noted, this case suggests that a child's liver may be less vulnerable to the hepatotoxic effects of acetaminophen overdose than an adult's. The agency points out, however, that before conclusions can be made on the potential toxicity of acetaminophen in children, more data are needed on the metabolism of acetaminophen and clinical observations in children (Ref. 2).

Carloss (Ref. 3) reported the death of a 3½-year-old girl who had an upper respiratory infection and was being treated with acetaminophen. The child was given 120 mg of acetaminophen syrup every 4 hours for three doses. Her doctor later increased the dose to 720 mg every 3 hours. During the next 24 hours she took 5.04 g acetaminophen and was hospitalized for nausea and vomiting. Fourteen hours after the last dose, the acetaminophen level was 5.3 mg/dL (therapeutic range, 1 to 3 mg/dL), well in the range of hepatotoxicity. The child was discharged from the hospital the next morning, but was readmitted 16 hours later with a serum glutamic-oxaloacetic transaminase level of 22,000 I.U. and subsequently died.

The child described by Carloss (Ref. 3) was approximately the same age as the one described by Arena, Rourk, and Sibrack (Ref. 1). Neither child had been treated with an antidote for acetaminophen poisoning, such as *N*-acetylcysteine. It is difficult to explain why the child who had ingested 5.04 g acetaminophen died, and the child who had ingested 11.375 g acetaminophen survived.

Regarding chronic use of acetaminophen within recommended OTC dosages, the agency at this time does not believe that the labeling suggested by the comment, "Do not exceed recommended dosage or take for more than 10 days, because severe liver damage may occur," is needed. The warnings proposed in § 343.50(c) (1)(i) and (3) in this tentative final monograph already state a 10-day limitation for adults on OTC analgesic self-medication. Furthermore, the agency is aware of only one somewhat convincing case report of acetaminophen hepatotoxicity associated with chronic acetaminophen usage in a normal individual (Ref. 4). A second case has

been reported, but rechallenge results were inconsistent (Ref. 5). As discussed in detail in comment 27 below, Olsson (Ref. 4) described a 55-year-old male who was hospitalized for a flareup of hepatitis while taking a product containing acetaminophen and chlormezanone. He had no recent history of drug or alcohol use, but had a 1-year history of alcohol abuse 7 years before hospitalization. Because this individual developed hepatotoxicity on a low dose of acetaminophen, it is possible that some other problem was also present. (This patient was using a drug containing acetaminophen and chlormezanone, which could have induced the liver injury.) No similar report has appeared despite the wide use of acetaminophen.

A case of chronic use of 325 mg acetaminophen (12 tablets daily for 1 year) was described in which the patient's serum glutamic-oxaloacetic transaminase level was normal before acetaminophen use (Ref. 5). After 1 year of acetaminophen use, liver function tests showed an abnormal serum glutamic-oxaloacetic transaminase level and enlargement of the liver and spleen. After the drug was discontinued, the patient's serum glutamic-oxaloacetic transaminase level returned to normal. After being discharged from the hospital, the patient resumed using 12 tablets of 325 mg acetaminophen daily. Within 2 months he developed pain and was rehospitalized. A monitored rechallenge with one dose of 1,325 mg acetaminophen caused a rise in liver enzyme levels (serum glutamic-oxaloacetic transaminase and serum glutamic-pyruvic transaminase levels) within 12 to 18 hours. A liver biopsy revealed "bridging necrosis, spanning two portal and two central areas." After discontinuing acetaminophen for 4 months, the individual developed abdominal pain and enlargement of the spleen and had to be treated with azathioprine and prednisone. One year later, when liver function tests were back to normal, the individual again was rechallenged with 1,325 mg acetaminophen without any development of symptoms or rise in liver enzyme levels. This raises the possibility that this patient might have been developing chronic active hepatitis exacerbated by acetaminophen.

Rosenberg et al. (Ref. 6) described two individuals who had taken 3.6 g acetaminophen daily for 1 to 2 weeks. One person had a history of Gilbert's disease (characterized by mild jaundice). Both developed jaundice during a course of infectious mononucleosis. However, because

jaundice can occur in 5 to 10 percent of patients with infectious mononucleosis, the jaundice in these two patients could not definitely be attributed to acetaminophen.

Johnson and Tolman (Ref. 7) described a patient who had been taking 3 g acetaminophen daily and complained of fatigue and loss of appetite. The patient had used no other drugs and was not exposed to toxins other than unidentified cleaning solvents used occasionally. On medical examination there was liver tenderness, and a liver function test showed abnormal results. A liver biopsy revealed evidence of chronic active hepatitis with cirrhosis. The patient had a positive rechallenge, and the liver enzymes increased during the 2 weeks following the rechallenge, indicating that acetaminophen may have caused this elevation. It is possible that the patient had chronic active hepatitis and that acetaminophen exacerbated it. This case was also complicated by the concomitant occasional use of unidentified cleaning solvents.

The agency has noted instances where only a mild overdose of 5 to 7 g of acetaminophen may have produced hepatotoxicity. Ware et al. (Ref. 8) described a person who developed disorientation, jaundice, and fever after using acetaminophen and prescription drugs daily for headaches. Liver enzyme levels were elevated, and a liver biopsy showed centrilobular fibrosis and bridging necrosis with evidence of both an acute and a chronic process. The patient improved after 8 days of unspecified conservative treatment. This case does not prove acetaminophen hepatotoxicity because the other drugs the patient had been taking can cause hepatitis.

Toxic hepatitis was reported in three persons who were regularly ingesting acetaminophen in higher amounts than the recommended OTC dosage (Ref. 9). One patient was an alcoholic who for years had used up to 10 300-mg tablets of acetaminophen daily. During the 4 days before admission to the hospital, this individual drank no alcohol, but used about 100 tablets of acetaminophen. On admission to the hospital, the patient's liver enzymes were elevated, but they fell rapidly over the next 2 to 3 days. The amount of acetaminophen ingested and the subsequent pattern of serum liver enzyme abnormality found in this patient were consistent with a substantial overdose of acetaminophen 2 to 3 days before admission.

The second individual used as much as 5.2 g acetaminophen daily. This patient had disseminated bronchial

cancer, with general ill health and malnutrition. This patient's liver enzymes were elevated while using acetaminophen. After the liver enzymes returned to normal, the patient was rechallenged. The rechallenge of 5.2 to 6.5 g acetaminophen daily produced elevated liver enzyme levels. The plasma acetaminophen level at 24 hours was 37 µg/mL, corresponding to an overdose of the drug.

The third individual had reportedly used 5.2 to 6.5 g acetaminophen daily for 3 weeks before hospitalization. Forty hours after the last dose, the plasma acetaminophen concentration was 15 µg/mL, consistent with an overdose.

Although it is not inconceivable that chronic use of acetaminophen within recommended OTC dosage ranges produces chronic active hepatitis in a very low percentage of people, and although it is possible that acetaminophen can exacerbate preexisting chronic active hepatitis, the agency concludes that the above data do not provide an adequate basis for requiring a labeling statement on liver damage from chronic use of acetaminophen, that is, within recommended daily OTC dosages for longer than 10 days.

Although the liver warning recommended by the Panel in § 343.50(c)(5)(i) is being deleted, the agency shares the comments' concern that symptoms of acetaminophen toxicity do not appear until a few days after an overdose. Following acetaminophen overdosage, there is a 24- to 48-hour period of relative well-being, when symptoms of hepatotoxicity do not appear despite the occurrence of liver damage. This "silent period" may create a false sense of security that could delay the use of an antidote, which must be administered promptly in order to be effective (Refs. 10 and 11). To alert consumers that prompt medical attention is essential to the proper management of acetaminophen overdose, the agency is proposing the following overdose warnings for acetaminophen drug products: For products labeled for adults (§ 343.50(c)(1)(iii)), "Prompt medical attention is critical for adults as well as for children even if you do not notice any signs or symptoms," or for products labeled for children (§ 343.50(c)(2)(iii)), "Prompt medical attention is critical even if you do not notice any signs or symptoms." For products labeled both for adults and children, the warning for adults would apply, as described in § 343.50(c)(3). Both warnings would be required to follow the general overdose warnings in § 330.1(g) that are required for all OTC drugs.

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26. Several comments urged the adoption of a warning statement that advises consumers who have preexisting liver disease, such as hepatitis or infectious mononucleosis, or who may have Reye syndrome, against the use of acetaminophen unless directed by a doctor. The comments cited reports in the medical literature concerning acetaminophen toxicity in persons with liver disease (Refs. 1 through 13). Two comments asserted that there is no evidence to warrant a warning regarding acetaminophen and preexisting liver disease. One of these comments submitted two clinical studies (Refs. 14 and 15) and a report (Ref. 16) to support its position.

In reviewing and evaluating the data and information submitted by the comments, the agency has concluded that there is insufficient evidence at present to propose a warning against the use of acetaminophen at recommended OTC dosages by individuals with preexisting liver disease.

The data and information in Refs. 1 through 7, Refs. 9 through 13, and Ref. 16 presented no evidence to show that OTC dosages of acetaminophen cause

hepatotoxicity in persons with preexisting liver disease. Rosenberg et al. (Ref. 8) described two persons who developed jaundice during a course of infectious mononucleosis. As discussed in comment 25 above, the jaundice cannot be confidently ascribed to acetaminophen.

One of the clinical studies (Ref. 14) presents an open study of six male adults with chronic liver disease who were given 1 g acetaminophen every 4 hours four times a day. After 5 days of acetaminophen administration, there were no significant changes in liver enzyme laboratory values. The mean half-life of acetaminophen in these six subjects was  $3.42 \pm 2.5$ . Ten hours after an initial dose of 1 g acetaminophen was administered on the first day, the plasma acetaminophen level was  $1.9 \pm 1.5$   $\mu\text{g/mL}$ . There was no evidence of any significant accumulation of acetaminophen in the plasma of these individuals.

The other clinical study (Ref. 15) presents a placebo-controlled, double-blind, crossover study in which placebo or 4 g acetaminophen (1 g every 4 hours for four doses per day) was administered daily to 20 adults with preexisting liver disease of various types. The individuals were treated for 3 days and crossed over to the alternate regimen without a washout period. In comparing liver enzyme levels of the individuals during acetaminophen administration with those during placebo administration, no statistically significant differences were found. Three patients were excluded from the final analysis. One had changes in liver enzymes which could be attributed to the erratic course of his chronic active hepatitis. Although it is difficult to distinguish enzyme changes because of the erratic course of chronic active hepatitis versus drug-induced changes, the resulting rise in transaminases after rechallenge with acetaminophen raises the question of whether acetaminophen exacerbated this individual's chronic active hepatitis.

Additional data regarding the plasma half-life of acetaminophen in individuals with liver disease were presented at a meeting of FDA's Gastrointestinal Drugs Advisory Committee (Ref. 17). These data appeared to document prolonged serum half-life for acetaminophen in patients with liver disease. Nonetheless, the results of the placebo-controlled crossover study (Ref. 15) gave no evidence that this prolongation results in hepatotoxic levels of the drug. It should be pointed out, however, that prolonged acetaminophen half-life in the patients in this study was not

documented, and thus it is not certain that the patients were at risk for possible adverse effects related to such prolongation.

Data pertaining to cytochrome P-450 enzyme levels in patients with liver disease may also be relevant to determining acetaminophen hepatotoxicity. Available data attribute the production of the hepatotoxic metabolite of acetaminophen to the cytochrome P-450 system. A reduction in activity of the cytochrome P-450 system then might result in reduced risk of hepatotoxicity.

The following data show decreased cytochrome P-450 levels in individuals with chronic liver disease. Farrell, Cooksley, and Powell (Ref. 18) showed that the cytochrome P-450 concentrations in patients taking enzyme-inducing drugs such as phenobarbital, phenytoin, and glutethimide are no different in control subjects than in persons with mild-to-moderate hepatitis or inactive cirrhosis. The patients with severe hepatitis or active cirrhosis who were taking enzyme-inducing drugs did have decreased cytochrome P-450 concentrations and may have lost the ability to respond to inducing agents.

Schoene et al. (Ref. 19) measured the cytochrome P-450 content in needle biopsies of the human liver and found that in individuals with severe hepatitis and cirrhosis, the cytochrome P-450 level was 50 percent of the control value. In individuals with either mild or moderate hepatitis, there was no change in the cytochrome P-450 level. Gabrielle et al. (Ref. 20) found no change in the cytochrome P-450 content in individuals with alcoholic steatosis and in those recovering from viral hepatitis compared with normal individuals. The cytochrome P-450 level in chronic persistent hepatitis was 10 percent of the level in the normal individuals. In chronic active hepatitis, the cytochrome P-450 level was 30 percent of that of a normal individual. Although these data suggest that the activity of the cytochrome P-450 system is reduced in individuals with severe liver disease, the relevance of this finding to acetaminophen hepatotoxicity in such individuals is not clear. It is possible that low cytochrome P-450 levels would protect against acetaminophen hepatotoxicity, but the evidence is conflicting on whether acetaminophen exacerbates liver disease.

In summary, the agency believes that at present there are insufficient data to support a warning against the use of acetaminophen by persons with preexisting liver disease such as

hepatitis, liver function affected by infectious mononucleosis, or liver disease resulting from Reye syndrome.

#### References

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27. Several comments cited data to express concern that certain drugs which induce microsomal enzyme activity (e.g., alcohol and barbiturates) may increase the potential for acetaminophen-induced hepatotoxicity (Refs. 1 through 14). The comments recommended that warnings such as the following be required on the labeling of all products containing acetaminophen:

Do not take this product if you use alcohol or barbiturates unless directed by a physician.

Caution: Do not take this product if you are presently taking a prescription drug for epilepsy, barbiturates, or ethacrynic acid except under the advice and supervision of a physician.

A reply comment opposed the suggested warnings, stating that there is no evidence of any significant drug interaction of acetaminophen when used at recommended doses with drugs which induce microsomal enzyme activity.

The agency is not adopting the suggestion that consumers be warned against the use of ethacrynic acid with acetaminophen. The comments submitted no data to support such a warning, and the agency is not aware of data that indicate a need to warn consumers against the use of ethacrynic acid with acetaminophen.

After reviewing the data cited by the comments, the agency has determined that the results are conflicting and that there is insufficient evidence at this time to warrant a label warning against the use of OTC dosages of acetaminophen products with alcohol, barbiturates, or prescription drugs used for epilepsy.

One comment cited a commentary on acetaminophen which recommended that drugs such as phenobarbital and alcohol should not be used with acetaminophen because they appear to potentiate acetaminophen-induced hepatotoxicity (Ref. 1). However, no firsthand data were presented to support this recommendation. A report by Wilson et al. (Ref. 2) concerned a 13-year-old epileptic who took an overdose of acetaminophen and phenobarbital, subsequently developed hepatic encephalopathy, and died. These authors emphasized the seriousness of dealing with acetaminophen overdose, complicated in this case by the role of

phenobarbital in potentiating the hepatotoxicity of acetaminophen.

Wright and Prescott (Ref. 3) retrospectively analyzed data on 16 individuals with hepatic necrosis following acetaminophen overdose. Eight of these individuals showed evidence of ingestion of either alcohol or barbiturates used in the treatment of epilepsy. Three individuals were chronic alcoholics. Wright and Prescott stated that their findings suggest that acetaminophen causes more severe hepatic necrosis in patients who have previously taken drugs that may cause induction of hepatic microsomal enzymes, such as barbiturates and alcohol. However, they conceded that their results must be interpreted cautiously because of the small number of individuals studied and because of uncontrollable factors such as age and nutritional state of the individuals, as well as the possibility of their ingesting other drugs.

Mitchell et al. (Ref. 4) concluded, as a result of their studies in rats and mice, that pretreatment of these animals with phenobarbital potentiates both the incidence and the severity of acetaminophen-induced hepatic necrosis. However, Prescott (Ref. 5) conducted a study on acetaminophen metabolism in 12 healthy volunteers and 15 individuals who were chronically using microsomal enzyme-inducing agents such as phenobarbital and diphenylhydantoin, drugs used in treating epilepsy. Prescott concluded that the production of hepatotoxic metabolites of acetaminophen was not increased in those individuals who used hepatic enzyme-inducing agents. These studies have produced conflicting results which are difficult to reconcile and from which firm conclusions cannot be drawn.

Scott and Stewart (Ref. 6) reported that most of the cases of acetaminophen overdose which they had seen were accompanied by some alcohol use and said that the time available for effective treatment of overdose may be "much reduced" in individuals with alcohol-damaged livers. Barker, de Carle, and Anuras (Ref. 7) observed severe liver damage in an alcoholic who had ingested "moderately excessive" amounts of acetaminophen (100 tablets of 300 mg acetaminophen 4 days before admission to the hospital). These investigators concluded that this individual's use of alcohol induced the formation of toxic acetaminophen metabolites, which made him more susceptible to liver injury from the "moderately excessive" dose of acetaminophen.

Emby and Fraser (Ref. 8) reported on two cases of acetaminophen overdose in alcoholics and concluded that " \* \* \* the enhanced hepatotoxicity of paracetamol (acetaminophen) in the presence of enzyme-inducing agents \* \* \* has perhaps not been adequately emphasized." McClain et al. (Ref. 9) conducted studies in mice and also observed the clinical course of three chronic alcoholics who ingested therapeutic, rather than excessive, dosages of acetaminophen. McClain et al. stated that their findings " \* \* \* suggest that alcohol enhances acetaminophen hepatotoxicity in mice and provides supportive evidence that these three alcoholic patients probably had a similar pathophysiological basis for their liver disease." Goldfinger et al. (Ref. 10) reported hepatic damage in an alcoholic who had ingested 9.75 g acetaminophen over a 2-day period prior to hospitalization. Vilstrup et al. (Ref. 11) reported on fulminant liver failure in a woman who was a known abuser of alcohol, diazepam, and barbiturates. The woman had taken a total of 5.4 g acetaminophen over a 2-day period for premenstrual pain and subsequently died.

The agency points out that the amount of acetaminophen ingested by the woman described by Vilstrup et al. is subject to question. It is also difficult to determine the exact daily dosage of acetaminophen ingested by those individuals observed by McClain et al. (Ref. 9) and Goldfinger et al. (Ref. 10). However, it appears that the individuals reported on by McClain et al. and Goldfinger et al. had ingested more than 4 g acetaminophen, which is the recommended maximum daily OTC dosage. In addition, the individual observed by Goldfinger et al. was using meprobamate, another hepatic microsomal enzyme inducer, in addition to alcohol and acetaminophen.

Olsson (Ref. 12) described an individual who had a 1-year history of alcohol abuse (occurring 7 years before hospitalization) and who was hospitalized with jaundice, hepatic cholestasis, and hepatic steatosis. This individual was using a drug containing acetaminophen and chlormezanone. Olsson acknowledged that it was impossible to obtain a reliable drug history from the patient. The role of alcohol is unclear, and chlormezanone could have induced the liver injury seen in this individual. Furthermore, no plasma acetaminophen determination was performed on this individual. Thus it is difficult to implicate acetaminophen and alcohol use positively as the causative factors in this case.

Shamszad et al. (Ref. 13) compiled data that suggest that the half-life of acetaminophen is significantly prolonged in patients with liver disease from alcohol use. However, these investigators noted that when alcohol is used simultaneously with acetaminophen the plasma disappearance curve of acetaminophen is unchanged.

In considering the wide use of acetaminophen in the United States, and after evaluating the above data, the agency concludes that the evidence available to warrant a label warning against the use of OTC dosages of acetaminophen with barbiturates, prescription drugs for epilepsy, or alcohol is conflicting and insufficient. However, if additional data demonstrate the need for such warnings in the future, the agency will reconsider its present position.

#### References

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- (8) Emby, D., and B. Fraser, "Hepatotoxicity of Paracetamol Enhanced by Ingestion of Alcohol," *South African Medical Journal*, 51:208-209, 1977.
- (9) McClain, C.J., et al., "Potentiation of Acetaminophen Hepatotoxicity by Alcohol," *Journal of the American Medical Association*, 244:251-253, 1980.
- (10) Goldfinger, R., et al., "Concomitant Alcohol and Drug Abuse Enhancing Acetaminophen Toxicity," *American Journal of Gastroenterology*, 70:385-388, 1978.
- (11) Vilstrup, H., et al., "Liver Damage after Paracetamol," *Ugeskrift for Laeger*, 139:831-4, 1977.
- (12) Olsson, R., "Increased Hepatic Sensitivity to Paracetamol," *Lancet*, 2:152-153, 1978.

(13) Shamszad, M., et al., "Abnormal Metabolism of Acetaminophen in Patients with Alcoholic Liver Disease" (abstract), *Gastroenterology*, 69:865, 1975.

28. Citing reports in the literature (Refs. 1 through 9) to substantiate their argument, several comments stated that acetaminophen has many adverse effects that should be included in label warnings for products containing this ingredient. These adverse effects include allergic reactions with clinical signs such as skin rashes, drug-induced fever, or asthma attacks associated with cross-sensitivity between aspirin and acetaminophen. Other adverse effects include blood dyscrasias, which are abnormal conditions of the blood. An example is thrombocytopenia, a decrease in the number of platelets. The comments attributed these adverse effects either to allergic reactions or idiosyncratic reactions, which are abnormal reactions peculiar to the individual. They also recommended a label warning to advise consumers who are allergic to acetaminophen not to use products containing that drug, and a label warning to advise consumers who have asthma or are sensitive or allergic to aspirin to consult their physician before using acetaminophen drug products.

Two reply comments disagreed, arguing that clinical experience and the medical literature indicate that adverse effects from acetaminophen are rare and do not support the need for such warning statements. These comments also maintained that some of the references cited are single-case, anecdotal reports and that there is insufficient evidence in most of the cases to establish a cause-and-effect relationship between acetaminophen and the reported reactions.

The agency believes that the warnings which the comments requested are not warranted at this time because there is insufficient evidence that these adverse effects are being caused by acetaminophen. However, if sufficient evidence is presented to warrant new warnings in the future, the agency will act accordingly.

Two of the reports on adverse effects of acetaminophen cited by the comments had also been cited by the Panel and presented no new data for the agency's consideration (Refs. 3 and 4). Some of the reports cited by the comments were single-case reports of thrombocytopenia, which may have resulted from a number of factors, including idiosyncrasy, or which may have been caused by agents other than acetaminophen (Refs. 1, 3, and 7). There were three single-case reports of skin rash following the use of acetaminophen

(Refs. 4, 5, and 9), but no cases of drug-induced fever.

Studies present conflicting data on the occurrence of cross-sensitivity between aspirin and acetaminophen (Refs. 2, 6, 8, 10, and 11). Fisherman and Cohen's study (Ref. 2) contained five cases of cross-sensitivity between aspirin and acetaminophen. These researchers calculated an "intolerance index," which can be used to compare the tendency of various drugs to produce allergic reactions. The index is based on the usual therapeutic dose divided by the minimal dose needed to produce clinical symptoms of intolerance. This result is multiplied by the percent of patients showing intolerance. The calculated "intolerance index" of aspirin was 368 compared with 13.5 for acetaminophen, indicating that there is a low degree of cross-reactivity to acetaminophen in aspirin-sensitive patients.

The Smith study (Ref. 8) also contained five cases of cross-sensitivity between aspirin and acetaminophen. A challenge dose of several common analgesics was given to five aspirin-sensitive patients, two of whom indicated they were sensitive to acetaminophen. Smith measured the change in forced expiratory volume, which is a measure of air flow and pulmonary function, and noted whether rhinitis was present. Three of the patients had statistically significant drops in forced expiratory volume, and four patients also developed rhinitis following acetaminophen administration. This study indicates a potential problem in a person who is highly sensitive to aspirin and who uses analgesic drugs, including acetaminophen, but it does not explain the clinical significance of changes in the forced expiratory volume.

Other studies, not cited by the comments, found no sensitivity to acetaminophen among aspirin-sensitive patients (Refs. 10 and 11). Sampter and Beers (Ref. 10) tested acetaminophen in 182 aspirin-sensitive patients and found no adverse reactions. Other investigators tested 11 aspirin-sensitive patients with therapeutic doses of acetaminophen and found no reaction to acetaminophen (Ref. 11).

Because of the conflicting data on the incidence of cross-sensitivity between aspirin and acetaminophen, the agency is not proposing a warning about cross-sensitivity to other analgesics on the acetaminophen label. Although the potential for allergic reactions to acetaminophen does exist, the agency believes that the following statement in the warnings in § 343.50(c) (1)(i), (2)(i)

and (3) will adequately inform consumers to consult a doctor if an allergic reaction, such as a rash, should occur following the use of acetaminophen: "... if new symptoms occur ... consult a doctor because these could be signs of a serious condition."

#### References

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- (2) Fisherman, E.W., and G.N. Cohen, "Aspirin and Other Cross-Reacting Small Chemicals in Known Aspirin Intolerant Patients," *Annals of Allergy*, 31:476-84, 1973.
- (3) Heading, R.C., "Purpura and Paracetamol" (letter to the editor), *British Medical Journal*, 3:743-44, 1968.
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- (5) Michelson, P.A., "Rash, Weakness, and Acetaminophen," *Annals of Internal Medicine*, 83:374, 1975.
- (6) Schmid, W.H., "Acetaminophen-Induced Bronchospasm," *Southern Medical Journal*, 70:590 and 612, 1977.
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- (8) Smith, A.P., "Response of Aspirin-Allergic Patients to Challenge by Some Analgesics in Common Use," *British Medical Journal*, 2:494-496, 1971.
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- (10) Samter, M., and R.F. Beers, "Intolerance to Aspirin: Clinical Studies and Consideration of Its Pathogenesis," *Annals of Internal Medicine*, 63:975-983, 1968.
- (11) Szczeklik, A., R.J. Grylewski, and G. Czneriawska-Mysik, "Relationship of Inhibition of Prostaglandin Biosynthesis by Analgesics to Asthma Attacks in Aspirin-Sensitive Patients," *British Medical Journal*, 1:67-69, 1975.

29. One comment suggested that the professional labeling recommended by the Panel (§ 343.80) be revised to include the indications that the Panel did not place in Category I because of its concern about self-diagnosis. The comment argued that, although self-diagnosis is a valid concern for consumer-oriented labeling, this concern is irrelevant to professional labeling. Another comment suggested that the Panel's recommended warnings listed below be moved from consumer labeling to professional labeling because these statements refer to conditions that should be diagnosed and supervised by a physician. The comment concluded that these warnings are irrelevant to a consumer with an undiagnosed condition, and are not needed once the

condition is diagnosed because the consumer is then under the care of a physician who will recommend proper medication and advise against inappropriate medication.

The warnings recommended by the comment for inclusion in professional labeling are as follows:

*Section 343.50(c)(3)(i):* "Take this product for the treatment of arthritis only under the advice and supervision of a physician."

*Section 343.50(c)(3)(iv):* "Caution: Do not take this product if you have stomach distress, ulcers, or bleeding problems except under the advice and supervision of a physician."

*Section 343.50(c)(3)(v):* "Caution: Do not take this product if you are presently taking a prescription drug for anticoagulation (thinning the blood), diabetes, gout, or arthritis except under the advice and supervision of a physician."

*Section 343.50(c)(4)(i):* "This product contains aspirin. Do not take this product if you are allergic to aspirin or if you have asthma except under the advice and supervision of a physician."

*Section 343.50(c)(4)(ii):* "Do not take this product during the last 3 months of pregnancy except under the advice and supervision of a physician."

*Section 343.50(c)(4)(iii):* "Do not take this product for at least 7 days after tonsillectomy or oral surgery except under the advice and supervision of a physician."

The request made by the first comment did not specify the indications it was referring to; therefore, the agency cannot respond.

The agency disagrees with the second comment's suggestion that the warnings listed above be moved to the professional labeling section of the monograph. These warnings are essential for the safe and effective use by consumers of the products to which they apply (with the exception of § 343.50(c)(3)(i), which is being deleted for reasons stated in comment 19 above), and the agency proposes to require them in consumer labeling.

30. One comment stated that the following warnings recommended by the Panel in § 343.50(c) should be eliminated from OTC analgesic and antipyretic drug products that are marketed in children's dosage units as children's products: "Adults: Do not take this product for more than 10 days. If symptoms persist, or new ones occur, consult your physician." "Adults: Drink a full glass of water with each dose." "Do not take this product during the last 3 months of pregnancy except under the advice and supervision of a physician."

The comment contended that these statements, clearly intended for adults, are unnecessary and inappropriate for analgesic and antipyretic drug products labeled for children. The comment added that requiring these warnings on small containers (e.g., the 30-tablet size limitation for pediatric aspirin products) will result in smaller print that will make the labeling message less conspicuous, less legible, and less likely to be read and understood by the consumer.

The comment also stated that the words "Children under 12 years" should be eliminated from the recommended warnings in § 343.50(c)(1)(ii) and (c)(3)(iii)(b), for the reasons given above as well as the reason that the statement is superfluous because pediatric products are defined by the Panel in § 343.3(e) as products for children under 12 years.

The pregnancy warning recommended by the Panel in § 343.50(c)(4)(ii) is obviously not needed in products intended only for use in children. In addition, the pregnancy-nursing warning required for all OTC drugs intended for systemic absorption specifically provides for an exemption for drugs that are labeled exclusively for pediatric use. (See 21 CFR 201.63(c)(2).)

The agency agrees that the warnings for adults limiting use to not more than 10 days and directing them to drink a full glass of water with each dose (§ 343.50(c)(1)(i) and (c)(3)(iii)(a)) are unnecessary in the labeling of products intended only for use in children, as the warnings in § 343.50(c)(1)(ii) and (c)(3)(iii)(b) provide the necessary information for children under 12 years of age. The warnings recommended by the Panel in § 343.50(c)(1)(i) and (c)(1)(ii) are being revised and expanded into three warnings appearing in the tentative final monograph under the following sections: § 343.50(c)(1)(i), for products labeled for adults; § 343.50(c)(2)(i), for products labeled for children 2 years to under 12 years of age; and § 343.50(c)(3), for products labeled both for adults and for children 2 years to under 12 years of age. (See comment 18 above.)

The agency agrees that products that are clearly identified for use in children, e.g., infant drops, children's aspirin or acetaminophen tablets, do not have to be labeled with a statement in the warnings or in the directions specifying that they are for children under 12 years, as had been recommended by the Panel. Because the directions for use for such products do not include dosages for people over 12 years of age or under 2 years of age, further labeling specifying

that these products are intended for use by children from 2 to 12 years of age appears to be unnecessary. Accordingly, new § 343.50(b)(4) is being proposed in the tentative final monograph as follows:

(4) *Other required statements—(i) For products labeled only for children 2 to under 12 years of age containing any ingredient identified in § 343.10. (A) The labeling of the product contains, on the principal display panel, either of the following:*

(1) "Children's (trade name of product or generic name of ingredient(s))."

(2) "(Trade name of product or generic name of ingredient(s)) for Children."

(B) The labeling for adults in § 343.50(d) and the statement "Children 2 to under 12 years of age" in § 343.50(d)(3)(ii) are not required.

31. One comment supported and two comments opposed the part of the warning recommended by the Panel for aspirin drug products in § 343.50(c)(3)(iv) which states, " \* \* \* Do not take this product if you have stomach distress \* \* \* ."

The supporting comment stated that aspirin drug products cause gastrointestinal distress at therapeutic doses and that their labeling should bear a warning to this effect. The opposing comments recommended deleting the term "stomach distress," contending that it has little meaning to consumers. The term is so all-inclusive, the comment maintained, it may discourage consumers from using aspirin for symptoms for which it is indicated. The comments explained that "stomach distress" often accompanies symptoms such as headache or fever, as with the common cold or flu, and that the warning may discourage consumers from using aspirin for these concurrent symptoms. One comment suggested that, as alternative labeling, consumers be warned against the use of aspirin "in cases of stomach ulcer and related symptoms."

Because the agency shares the comments' concern that the general term "stomach distress" can be applied to various symptoms and may have little meaning to consumers, the agency is proposing to delete this term from the warning recommended by the Panel in § 343.50(c)(3)(iv).

Although the agency believes that alternative labeling is warranted, it is not adopting the alternative labeling suggested by one of the comments because the term "related symptoms" is vague and probably has little meaning to consumers. As the Panel pointed out, plain aspirin products can cause stomach discomfort or "stomach problems," such as heartburn, upset

stomach, or stomach pain, in certain individuals (42 FR 35387). Plain aspirin can also exert adverse effects on the gastrointestinal tract (i.e., mucosal erosion, ulceration, minor occult bleeding, etc.) which may exacerbate stomach problems associated with underlying gastrointestinal disease. These effects can also be produced by salicylates other than aspirin (42 FR 35417 to 35421).

Regarding buffered aspirin products, the Panel stated that " \* \* \* evidence seems to indicate that buffered aspirin produces a lower incidence of gastric intolerance in some patients but not in all patients who exhibit gastric intolerance with regular (plain) aspirin products" (42 FR 35470). However, the agency notes that the Panel also stated that this evidence is conflicting. In addition, the investigators of another study on the incidence of gastric lesions in rheumatic patients using plain, buffered, or enteric-coated aspirin concluded that buffered aspirin with an acid-neutralizing capacity of 1.9 milliequivalents (mEq) per 325 mg aspirin did not appear to prevent aspirin-induced gastric damage (Ref. 1). However, these investigators stated that more definitive studies are needed which compare various aspirin preparations before any final conclusions are reached.

Another study showed that OTC doses of buffered aspirin tablets containing 6.4 mEq of antacid, which exceeds the amount of buffering present in most currently marketed buffered aspirin products, produced gastric mucosal injury. The investigators of this study concluded that such products offer little protection to the gastric and duodenal mucosa (Ref. 2). Furthermore, the Panel stated that there is evidence that highly buffered aspirin for solution will reduce, but not eliminate, the acute gastric erosions and occult blood loss produced by the local effects of aspirin in animals and humans with no predisposing gastrointestinal disease (42 FR 35471).

For these reasons, the agency tentatively concludes that it is necessary to advise consumers who have persistent or recurring stomach problems (such as heartburn, upset stomach, or stomach pain), which may be symptoms of an underlying gastrointestinal disorder, against using products containing aspirin (plain or buffered) or other salicylates unless directed by a doctor. Accordingly, the Panel's recommended warning in § 343.50(c)(3)(iv) (redesignated § 343.50(c)(1)(v)(B)) is being revised as follows: "Do not take this product if you have stomach problems (such as

heartburn, upset stomach, or stomach pain) that persist or recur, or if you have ulcers or bleeding problems, unless directed by a doctor." This warning is also being revised in § 343.50(c)(2)(v)(B) for products labeled for children 2 years to under 12 years of age.

#### References

(1) Silvano, G.R., et al., "Incidence of Gastric Lesions in Patients with Rheumatic Disease on Chronic Aspirin Therapy," *Annals of Internal Medicine*, 91:517-520, 1979.

(2) Lanza, F.L., G.L. Royer, Jr., and R.S. Nelson, "Endoscopic Evaluation of the Effects of Aspirin, Buffered Aspirin, and Enteric-Coated Aspirin on Gastric and Duodenal Mucosa," *New England Journal of Medicine*, 303:136-138, 1980.

32. One comment asserted that warning statements for aspirin drug products should be stated separately. The comment stated that the following warning is the most important warning to the consumer and should be displayed alone on the label so that its effect is not diminished: "Warning: Keep this and all medicines out of children's reach. In case of accidental overdose, contact a physician immediately." The comment stated that all other cautions on the use of aspirin drug products should be under a section designated "Cautions."

The agency agrees that the general warnings quoted above are among the most important provided for all OTC drugs to consumers. These warnings are required for OTC drug products in § 330.1(g) (21 CFR 330.1(g)). The agency agrees that manufacturers should consider displaying these warnings separately from other label warnings or highlighting them to attract consumers' attention.

Concerning the use of the terms "warning" and "caution," section 502(f)(2) of the Federal Food, Drug, and Cosmetic Act (the act) (21 U.S.C. 352(f)(2)) states, in part, that any drug marketed OTC must bear in labeling " \* \* \* such adequate warnings \* \* \* as are necessary for the protection of users \* \* \* ." Section 330.10(a)(4)(v) of the OTC drug regulations provides that labeling of OTC drug products should include " \* \* \* warnings against unsafe use, side effects, and adverse reactions \* \* \* ."

The agency notes that historically there has not been consistent usage of the signal words "warning" and "caution" in OTC drug labeling. For example, in §§ 369.20 and 369.21 (21 CFR 369.20 and 369.21), which list "warning" and "caution" statements for drugs, the signal words "warning" and "caution" are both used. In some instances either

of these signal words is used to convey the same or similar precautionary information.

FDA has considered which of these signal words would be most likely to attract consumers' attention to that information describing conditions under which the drug product should not be used or its use should be discontinued. The agency concludes that the signal word "warning" is more likely to flag potential dangers so that consumers will read the information being conveyed. Therefore, FDA has determined that the signal word "warning," rather than the word "caution," will be used routinely in OTC drug labeling that is intended to alert consumers to potential safety problems. Accordingly, the signal word "caution" is being deleted from the Panel's recommended warnings in § 343.50(c)(3) (iv) and (v), redesignated § 343.50(c)(1)(v) (B) and (C) in this proposed monograph.

33. One comment stated that the first sentence of the aspirin hypersensitivity warning recommended in § 343.50(c)(4)(i), "This product contains aspirin," is redundant for products that display the word "aspirin" in the product name or are clearly labeled as containing "aspirin." The comment stated that part of the next sentence in the warning, "Do not take this product if you are allergic to aspirin . . ." is adequate to warn consumers and that the first sentence should be deleted.

The agency agrees with the comment. Because section 502(e)(1) of the act (21 U.S.C. 352(e)(1)) requires that the established name of the active ingredients contained in a product be included in the label, the statement, "This product contains aspirin," would be redundant. Therefore, in the tentative final monograph this statement is being deleted from the warning.

34. Two comments urged that all children's aspirin products be labeled to include a warning that salicylate intoxication can occur from a therapeutic overdose when "aspirin is repetitively administered to infants and young children at commonly recommended doses and time intervals." The comments argued that parents have been inadequately alerted to the hazards associated with the cumulative effects of salicylate in infants and young children and that parents frequently ignore recommended dosage schedules for aspirin because they think this drug can be administered with relative impunity. The comments further argued that parents will often continue to give aspirin to relieve a child's fever when the fever actually may be due to aspirin toxicity. One comment noted that ringing in the ears

(tinnitus) has no value as a warning of toxicity in the pediatric age group because it is subjective, and infants and young children cannot alert the parent to its occurrence. For these reasons the following warning was suggested for all aspirin drug products for children: "Do not exceed recommended doses unless directed by your physician. More than six consecutive doses at four-hour intervals can lead to serious complications in a feverish dehydrated infant or young child."

Two reply comments disagreed with these comments. One argued that the Panel's pediatric dosage schedule and its recommended warnings in § 343.50(c)(1)(ii) and (c)(2) contain instructions that, when heeded by parents, are adequate to prevent overdosage. These comments also stated that overdoses may occur with any drug and that parents must be alerted not to exceed the recommended dosages of aspirin as well as other drugs. The comments agreed that tinnitus has no value as a warning symptom because it cannot be adequately described by infants and children. However, the comments pointed out that there are observable symptoms of aspirin toxicity, such as hyperpnea, which can be described in labeling as "deep and rapid breathing." The reply comments also stated that dehydration should not be included in the labeling because parents cannot diagnose this condition, which is rare and should be diagnosed by a doctor. The comments also maintained that such labeling would confuse the consumer and obscure other necessary information on the label.

The agency does not believe that children's aspirin drug products should be labeled with a warning stating that salicylate intoxication can occur when aspirin is taken in doses within the recommended dosage schedule (therapeutic overdose). The reports of overdose of salicylates cited by the comments showed that poisoning from accidental ingestion occurs more commonly in children over 2 years of age and that therapeutic overdose is more likely to affect children under 2 years of age (Refs. 1, 2, and 3). The label directions recommended by the Panel for aspirin state, "For children under 2 years of age, there is no recommended dosage except under the advice and supervision of a physician." Thus, parents are alerted to consult a physician before giving aspirin to children under 2 years of age. The physician is responsible for giving parents specific dosage instructions for aspirin given to children under 2 years of age and for warning parents of the

potential dangers of exceeding the recommended dose.

For children 2 years of age and older, the Panel developed a new dosage schedule to help prevent therapeutic salicylate overdose. This dosage schedule not only is based upon a maximal dose that provides effective plasma levels for analgesic and antipyretic effects, but also has a safety margin in case of an inadvertent 50-percent increase in dosage. The agency believes that this children's dosage schedule, which has been slightly revised (see comment 58 below), and the revised warnings in § 343.50(c) (2)(i) and (3) provide adequate guidance to parents to prevent overdosage.

As for the additional labeling suggested by the comments, the agency believes that terms such as "dehydrated" and "deep and rapid breathing" have little meaning to consumers and are not appropriate for consumer labeling of aspirin drug products, although they may be used by doctors in diagnosing conditions due to toxicity. The information in the suggested labeling, "Do not exceed recommended doses unless directed by your physician," is provided in the directions for use by the phrase "or as directed by a doctor" or "unless directed by a doctor" after the usual recommended OTC dosage of the product.

#### References

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- (2) Done, A.K., and A.R. Temple, "Treatment of Salicylate Poisoning," *Modern Treatment*, 8:528-551, 1971.
- (3) Tschetter, P.N., "Salicylism," *American Journal of Diseases of Children*, 106:134-146, 1963.

35. One comment contended that the warning not to take aspirin if taking a prescription drug for arthritis should not be included in the Panel's recommended warning in § 343.50(c)(3)(v). The comment further contended that the major responsibility of warning the consumer of drug interactions should rest with the prescribing physician and that the following statement by the Panel (42 FR 35372) should apply: ". . . physicians always carefully control the patient's use of all other medications, thereby negating the need for a warning."

The agency believes that many consumers who take prescription drugs will also use OTC analgesics and antipyretics, such as salicylates, without a physician's advice. These consumers may be unaware of possible interactions between the salicylates and prescription

drugs and need to be alerted to this possibility in the labeling. Based upon the Panel's discussion of the increased potential for gastric ulceration if aspirin is taken along with another anti-inflammatory agent (42 FR 35409), the agency tentatively concludes that the warning on the concurrent use of salicylates with prescription drugs for arthritis is needed and therefore should be retained. The warning is not intended to prohibit such concurrent use, but to alert consumers to consult a doctor first.

36. Two comments objected to the Panel's recommended warning in § 343.50(c)(3)(v) that advises against the use of salicylates concurrently with prescription drugs for the treatment of gout. The comments asserted that the warning should be modified to apply only to the use of salicylates and uricosuric drugs, which are drugs that promote the excretion of uric acid in the urine. The comments argued that allopurinol, commonly prescribed for gout, is a nonuricosuric drug and is compatible with salicylates.

The agency endorses the labeling recommended in § 343.50(c)(3)(v) to alert consumers to consult a physician before using OTC salicylates with several types of prescription drugs, including those used in the treatment of gout. The agency concludes that differentiating between uricosuric and nonuricosuric drugs in the warnings for OTC salicylate drug products would be meaningless and confusing to consumers. Because the agency believes that it is important for consumers to understand the reason for this warning, it is proposing in the tentative final monograph that the information in § 343.50(c)(3)(v) (redesignated § 343.50(c)(1)(v)(C) in this monograph) be identified as a drug interaction precaution and appear as follows: "*Drug Interaction Precaution.* Do not take this product if you are taking a prescription drug for anticoagulation (thinning the blood), diabetes, gout, or arthritis unless directed by a doctor." This precaution has been modified in § 343.50(c)(2)(v)(C) for products labeled for children 2 years to under 12 years of age. For products labeled both for adults and children, the precaution for adults will apply. (See § 343.50(c)(3).)

37. One comment objected to the warning recommended by the Panel for aspirin and salicylate products in § 343.50(c)(3)(v), asserting that the potential for drug interaction is greater than that expressed in this labeling. The comment explained that because the information on drug interactions is increasing, the consumer who is using prescription medication should consult a

physician before using any pain reliever. The comment suggested the following alternative labeling, explaining that it is broader and more inclusive than the Panel's labeling and will provide safer coverage to the consumer: "If you are taking any prescription medication, consult your physician before using any pain reliever."

Another comment suggested the general drug interaction warning, "If you are taking any prescription medications, consult your physician before taking this medication."

The agency believes the labeling suggested by the comments is too general, and consumers might completely ignore its message. In addition, the suggested warnings would not alert consumers to the specific types of drugs that may interact with OTC analgesics. As discussed in comment 35 above, the agency will propose specific drug interaction warnings to consumers when necessary for the safe use of an OTC drug product.

38. Some comments opposed and others favored the Panel's recommended warning in § 343.50(c)(4)(i) against the use of aspirin drug products by consumers who have asthma. The opposing comments stated that the references the Panel cited to support the need for the warning were outdated and included no reports of fatal asthma attacks. The comments argued that the warning is unnecessary because only about 2 percent of asthmatics experience an adverse reaction to aspirin. Asthmatics are under a doctor's care, the comments stated, and the doctor should warn them of possible adverse reactions.

A comment from a consumer, who suffers from asthma and had been unaware that aspirin could precipitate asthma attacks, supported the Panel's warning. The comment insisted that it is necessary to warn asthmatics who may also be unaware that an asthma attack may occur with the use of aspirin drug products. Another supporting comment suggested the following alternative warning to avoid creating consumer anxiety: "If you have asthma \* \* \* consult your physician before using any pain reliever."

The agency is proposing the following warning in § 343.50(c)(1)(iv) for products containing aspirin or carbaspirin calcium: "Do not take this product if you are allergic to aspirin or if you have asthma unless directed by a doctor." The Panel stated that aspirin has long been associated with allergic-type reactions, such as asthma in hypersensitive individuals. In certain instances these reactions can be life-

threatening and even fatal (42 FR 35397). The consumer's comment reaffirmed the need to warn asthmatic consumers who may not always be alerted to this danger by a doctor.

The agency is not proposing the warning suggested by one comment because it refers to "any pain reliever" and is thus too broad. The medical literature includes a few reports that certain pain relievers other than aspirin may precipitate asthmatic attacks in aspirin-sensitive patients. However, these reports do not agree on the analgesic drugs implicated and the mechanism of action involved (Refs. 1 through 7). The agency concludes that more data and information are needed to determine the need for an asthma warning for pain relievers other than aspirin drug products.

#### References

- (1) "Analgesics and Asthma," *British Medical Journal*, 3:419-420, 1973.
- (2) Assem, E.S.K., "Immunological and Non-Immunological Mechanisms of Some of the Desirable and Undesirable Effects of Anti-Inflammatory and Analgesic Drugs," *Agents and Actions*, 6:212-218, 1976.
- (3) Fisherman, E.W., and G.N. Cohen, "Aspirin and Other Cross-Reacting Small Chemicals in Known Aspirin Intolerant Patients," *Annals of Allergy*, 31:476-484, 1973.
- (4) Smith, A. P., "Response of Aspirin-allergic Patients to Challenge by Some Analgesics in Common Use," *British Medical Journal*, 2:494-496, 1971.
- (5) Szczeklik, A., R. J. Gryglewski, and G. Czerniawska-Mysik, "Relationship of Inhibition of Prostaglandin Biosynthesis by Analgesics to Asthma Attacks in Aspirin-Sensitive Patients," *British Medical Journal*, 1:67-69, 1975.
- (6) Szczeklik, A., and C. Czerniawska-Mysik, "Prostaglandins and Aspirin-Induced Asthma" (letter to the editor), *Lancet* 1:488, 1976.
- (7) Weinberger, M., "Analgesic Sensitivity in Children With Asthma," *Pediatrics*, 62:910-915, 1978.

39. One comment disagreed with the wording in the Panel's recommended warning for aspirin and other salicylate products in § 343.50(c)(3)(ii), "Stop taking this product if ringing in the ears or other symptoms occur." The comment argued that the consumer should not be advised to stop taking the product if tinnitus develops because many doctors use tinnitus as a guideline for adjusting a patient's dosage level of aspirin to a therapeutically effective and tinnitus-free level. The comment stated that the phrase "or other symptoms occur" should be deleted from the warning because it is vague and confusing to the consumer. The comment suggested the following alternative: "If ringing in the

ears develops, consult your physician before taking any more medication."

The agency agrees that it is more appropriate to direct consumers with tinnitus to consult a doctor before taking more medication than to "stop taking" the product. The warning is being revised accordingly in the tentative final monograph. In addition, the phrase "or other symptoms occur" is being deleted from the warning because this phrase is synonymous with the phrase "if new symptoms occur," which has been included in the warnings in § 343.50(c)(1)(i), (2)(i), and (3).

The Panel noted that because aspirin or other salicylates produce a reversible ototoxicity manifested by deafness, it is important that patients who are regularly receiving salicylates at higher dosages be monitored by a physician for hearing loss as well as tinnitus. It is particularly important that patients with preexisting hearing loss be frequently monitored because they will not report tinnitus as plasma salicylate levels increase to toxic levels. An example of this was shown in a report from a consumer with a preexisting hearing loss who described a severe additional loss of hearing after using 50 grains (3,250 mg) of enteric-coated aspirin daily for a month (Ref. 1).

In view of the above considerations, the agency proposes to revise the warning, "Stop taking this product if ringing in the ears or other symptoms occur," to read as follows in § 343.50(c)(1)(v)(A) and (2)(v)(A): "If ringing in the ears or a loss of hearing occurs, consult a doctor before taking (giving) any more of this product."

#### Reference

(1) Letter from a consumer, included in OTC Volume 03BTFM.

40. One comment suggested that the term "bleeding problems" in the Panel's recommended warning in § 343.50(c)(3)(iv) be changed to "blood clotting problem." The comment argued that the term "blood clotting problem" is more accurate medically and would be more useful to consumers than "bleeding problems," which could be interpreted to include a minor cut that bleeds somewhat longer than usual. The comment provided three references to support its position (Refs. 1, 2, and 3).

The references provided by the comment do not suggest that the term "blood clotting problem" has more meaning to consumers than the term "bleeding problems." Two discuss bleeding time and other laboratory measurements (Refs. 1 and 2); the third discusses the side effect of gastrointestinal bleeding from aspirin use (Ref. 3).

The agency believes that the term "bleeding problems" as used in the warning in § 343.50(c)(3)(iv) (redesignated § 343.50(c)(1)(v)(B)) is accurate and useful to consumers. The Panel recommended the wording in this section to warn persons who have bleeding problems that they should not take aspirin except under the advice and supervision of a physician. Persons with bleeding problems such as hemophilia, von Willebrand's disease, thrombosthenia, or thrombocytopenia may react to aspirin drug products with a markedly prolonged bleeding time that might lead to a significant loss of blood in the gastrointestinal tract or elsewhere.

#### References

(1) Ingelfinger, F. J., "The Side Effects of Aspirin," *New England Journal of Medicine*, 290:1195-1197, 1974.

(2) Kaneshiro, M. M., et al., "Bleeding Time After Aspirin in Disorders of Intrinsic Clotting," *New England Journal of Medicine*, 281:1039-1042, 1969.

(3) Sanfelippo, M. J., and C. V. Hussey, "Thrombopathy; Identification and Distribution," *American Journal of Clinical Pathology*, 61:628-638, 1974.

41. One comment urged that the labeling of aspirin tablets direct consumers to take these products with food or milk. The comment personally attributed an incident of gastrointestinal bleeding to taking aspirin tablets with water rather than with milk or food, and maintained that food or milk would have coated the stomach and prevented the bleeding.

The comment submitted no data to support its viewpoint. The Panel considered whether salicylates should be taken with food, but concluded that it was most important that solid, oral dosage forms containing salicylates be taken with water to lessen the chance of gastric irritation (42 FR 35356). In fact, the Panel recommended the following warnings in § 343.50(c)(3)(iii): (a) "Adults: Drink a full glass of water with each dose," and (b) "Children under 12 years: Drink water with each dose."

The Panel specified a full glass of water for adults for each dose of salicylates. At gastric pH, 8 ounces or more of water is required to dissolve a dose of aspirin, the most commonly used salicylate. Undissolved salicylate in contact with the gastric mucosa is one cause of gastric irritation following salicylate ingestion. Although salicylate solution is less irritating than undissolved salicylate, the solution could also be irritating to the highly sensitive individual (42 FR 35387). Solid foods would delay the dissolution of salicylates, allowing the undissolved salicylate to remain in contact with the

gastric mucosa longer, but liquid foods, such as juice or milk, dissolve salicylate. However, the agency is concerned that, because of their acidity, taking some juices with aspirin may cause more irritation to the stomach than taking aspirin with water. Also, the agency is unaware of any data showing that milk will lessen the gastric irritation caused by aspirin. Therefore, the agency concurs with the Panel that consumers should be advised to take solid, oral dosage forms of salicylates with water to lessen the chance of gastric irritation. The agency believes that these statements belong under the directions for use, rather than in the warnings. Consequently the warnings recommended by the Panel in § 343.50(c)(3)(iii) (a) and (b) have been designated as directions in § 343.50(d)(3)(i) and (ii) of this tentative final monograph.

42. Two comments urged Category II status for the following labeling claims for buffered aspirin: "Buffering agents to help make the pain reliever more gentle to the stomach," "helps prevent the stomach upset often caused by plain aspirin," " \* \* \* provides ingredients that may prevent the stomach distress that plain aspirin occasionally causes but should not be taken by certain individuals with stomach disorders as cautioned elsewhere on the label," "faster to the bloodstream than plain aspirin," and claims implying more rapid analgesia as a result of an increased absorption rate.

The comments pointed out that the Panel concluded that there is insufficient evidence to substantiate the claims that buffered aspirin or highly buffered aspirin for solution (aspirin and antacid) can be safely used by persons who should not use plain aspirin. The comments stated that these claims may lead consumers to think that buffered aspirin products either give faster or greater pain relief than plain aspirin or cause less or no stomach distress. The comments expressed concern that reliance on claims relating to less stomach distress with buffered aspirin products could lead to a clinical danger in alcoholics and in persons who are prone to ulcers. Referring to claims such as "gets to the bloodstream faster than plain aspirin," the comments argued that blood level studies do not constitute acceptable scientific evidence to show that buffered products of this type are therapeutically superior to plain aspirin.

Other comments urged Category I status for the above labeling claims for buffered aspirin, stating that consumers should be informed of the purpose of buffering, and requested that the agency

The agency has examined the economic consequences of this proposed rulemaking in conjunction with other rules resulting from the OTC drug review. In a notice published in the Federal Register of February 8, 1983 (48 FR 5806), the agency announced the availability of an assessment of these economic impacts. The assessment determined that the combined impacts of all the rules resulting from the OTC drug review do not constitute a major rule according to the criteria established by Executive Order 12291. The agency therefore concludes that no one of these rules, including this proposed rule for OTC internal analgesic, antipyretic, and antirheumatic drug products, is a major rule.

The economic assessment also concluded that the overall OTC drug review was not likely to have a significant economic impact on a substantial number of small entities as defined in the Regulatory Flexibility Act, Pub. L. 96-354. That assessment included a discretionary Regulatory Flexibility Analysis in the event that an individual rule might impose an unusual or disproportionate impact on small entities. However, this particular rulemaking for OTC internal analgesic, antipyretic, and antirheumatic drug products is not expected to pose such an impact on small businesses. Therefore, the agency certifies that this proposed rule, if implemented, will not have a significant economic impact on a substantial number of small entities.

The agency invites public comment regarding any impact that this rulemaking would have on OTC internal analgesic, antipyretic, and antirheumatic drug products. Types of impact may include, but are not limited to, costs associated with product testing, relabeling, repackaging, or reformulating. Comments regarding the impact of this rulemaking on OTC internal analgesic, antipyretic, and antirheumatic drug products should be accompanied by appropriate documentation. Because the agency has not previously invited specific comment on the economic impact of the OTC drug review on internal analgesic, antipyretic, and antirheumatic drug products, a period of 180 days from the date of publication of this proposed rulemaking in the Federal Register will be provided for comments on this subject to be developed and submitted. The agency will evaluate any comments and supporting data that are received and will reassess the economic impact of this rulemaking in the preamble to the final rule.

The agency has determined that under 21 CFR 25.24(c)(6) this action is of a type that does not individually or cumulatively have a significant effect on the human environment. Therefore, neither an environmental assessment nor an environmental impact statement is required.

Sections 343.50(c)(1)(viii)(A) and 343.50(c)(2)(viii)(A) of this proposed rule contain collection of information requirements. As required by section 3504(h) of the Paperwork Reduction Act of 1980, FDA has submitted a copy of this proposed rule to the Office of Management and Budget (OMB) or its review of these collection of information requirements. Other organizations and individuals desiring to submit comments on the collection of information requirements should direct them to FDA's Dockets Management Branch (address above) and to the Office of Information and Regulatory Affairs, OMB, Rm. 3208, New Executive Office Bldg., Washington, DC 20503, Attn: Shannah Koss.

Interested persons may, on or before May 16, 1989, submit to the Dockets Management Branch (HFA-305), Food and Drug Administration, Rm. 4-62, 5600 Fishers Lane, Rockville, MD 20857, written comments, objections, or requests for oral hearing before the Commissioner on the proposed regulation. A request for an oral hearing must specify points to be covered and time requested. Written comments on the agency's economic impact determination may be submitted on or before May 16, 1989. Three copies of all comments, objections, and requests are to be submitted, except that individuals may submit one copy. Comments, objections, and requests are to be identified with the docket number found in brackets in the heading of this document and may be accompanied by a supporting memorandum or brief. Comments, objections, and requests may be seen in the office above between 9 a.m. and 4 p.m., Monday through Friday. Any scheduled oral hearing will be announced in the Federal Register.

Interested persons, on or before November 16, 1989, may also submit in writing new data demonstrating the safety and effectiveness of those conditions not classified in Category I. Written comments on the new data may be submitted on or before January 16, 1990. These dates are consistent with the time periods specified in the agency's final rule revising the procedural regulations for reviewing and classifying OTC drugs, published in the Federal Register of September 29, 1981

(46 FR 47730). Three copies of all data and comments on the data are to be submitted, except that individuals may submit one copy, and all data and comments are to be identified with the docket number found in brackets in the heading of this document. Data and comments should be addressed to the Dockets Management Branch (HFA-305) (address above). Received data and comments may also be seen in the office above between 9 a.m. and 4 p.m., Monday through Friday.

In establishing a final monograph, the agency will ordinarily consider only data submitted prior to the closing of the administrative record on January 16, 1990. Data submitted after the closing of the administrative record will be reviewed by the agency only after a final monograph is published in the Federal Register unless the Commissioner finds good cause has been shown that warrants earlier consideration.

#### List of Subjects

##### 21 CFR Part 310

Administrative practice and procedure, Drugs, Prescription exemption.

##### 21 CFR Part 343

Internal analgesics, Labeling, Over-the-counter drugs.

##### 21 CFR Part 369

Labeling, Over-the-counter drugs, Warning and caution statements.

Therefore, under the Federal Food, Drug, and Cosmetic Act and the Administrative Procedure Act, it is proposed that Subchapter D of Chapter I of Title 21 of the Code of Federal Regulations be amended as follows:

#### PART 310—NEW DRUGS

1. The authority citation for 21 CFR Part 310 is revised to read as follows:

Authority: Secs. 501, 502, 503, 505, 701, 704, 705, 52 Stat. 1049-1053 as amended, 1055-1056 as amended, 67 Stat. 477 as amended, 52 Stat. 1057-1058 (21 U.S.C. 351, 352, 353, 355, 371, 374, 375); 5 U.S.C. 553; 21 CFR 5.10 and 5.11.

##### § 310.201 [Amended]

2. In Subpart C, § 310.201 *Exemption for certain drugs limited by new-drug applications to prescription sale* is amended by removing paragraph (a)(1) and reserving it.

3. Part 343 is added to read as follows:

**PART 343—INTERNAL ANALGESIC, ANTIPYRETIC, AND ANTIRHEUMATIC DRUG PRODUCTS FOR OVER-THE-COUNTER HUMAN USE**

**Subpart A—General Provisions**

Sec.

343.1 Scope.

343.3 Definitions.

**Subpart B—Active Ingredients**

343.10 Analgesic-antipyretic active ingredients.

343.20 Permitted combinations of active ingredients.

**Subpart C—Labeling**

343.50 Labeling of analgesic-antipyretic drug products.

343.60 Labeling of permitted combinations of active ingredients.

343.80 Professional labeling.

**Subpart D—Testing Procedures**

343.90 Dissolution Testing.

Authority: Secs. 201(p), 502, 505, 701, 52 Stat. 1041-1042 as amended, 1050-1053 as amended, 1055-1056 as amended by 70 Stat. 919 and 72 Stat. 948 (21 U.S.C. 321(p), 352, 355, 371); 5 U.S.C. 553; 21 CFR 5.10 and 5.11.

**Subpart A—General Provisions**

**§ 343.1 Scope.**

(a) An over-the-counter analgesic-antipyretic drug product in a form suitable for oral administration is generally recognized as safe and effective and is not misbranded if it meets each of the conditions in this part in addition to each of the general conditions established in § 330.1 of this chapter.

(b) References in this part to regulatory sections of the Code of Federal Regulations are to Chapter I of Title 21 unless otherwise noted.

**§ 343.3 Definitions.**

As used in this part:

*Analgesic-antipyretic drug.* An agent used to alleviate pain and to reduce fever.

**Subpart B—Active Ingredients**

**§ 343.10 Analgesic-antipyretic active ingredients.**

The active ingredients of the product consist of any of the following when used within the dosage limits established for each ingredient in § 343.50(d):

(a) Acetaminophen.

(b) *Aspirin ingredients.* (1) Aspirin.

(2) Buffered aspirin. Aspirin identified in paragraph (b)(1) of this section may be buffered with any antacid ingredient(s) identified in § 331.11 of this chapter provided that the finished product contains at least 1.9 milliequivalents of acid-neutralizing

capacity per 325 milligrams of aspirin in accordance with § 331.26 of this chapter.

(c) Carbaspirin calcium.

(d) Choline salicylate.

(e) Magnesium salicylate.

(f) Sodium salicylate.

**§ 343.20 Permitted combinations of active ingredients.**

The following combinations are permitted provided each active ingredient is present within the established dosage limits and the product is labeled in accordance with § 343.60. Combinations containing aspirin must also meet the standards of an acceptable dissolution test, as set forth in § 343.90.

(a) *Combinations of acetaminophen with other analgesic-antipyretic active ingredients.* Acetaminophen identified in § 343.10(a) may be combined with any one ingredient listed below provided that each dose of the product contains 325 to 500 milligrams acetaminophen and the amount of the other ingredient as follows and provided that the product is not labeled for use by children under 12 years of age:

(1) Aspirin 325 to 500 milligrams.

(2) Carbaspirin calcium 414 to 637 milligrams.

(3) Choline salicylate 435 to 669 milligrams.

(4) Magnesium salicylate 377 to 580 milligrams.

(5) Sodium salicylate 325 to 500 milligrams.

(b) *Combinations of analgesic-antipyretic active ingredients with nonanalgesic-nonantipyretic active ingredients—*(1) *Acetaminophen and antacid combinations.* Acetaminophen identified in § 343.10(a) may be combined with any antacid ingredient identified in § 331.11 of this chapter or any combination of antacids permitted in accordance with § 331.10(a) of this chapter provided that the finished product meets all the requirements of § 331.10 of this chapter and bears labeling indications in accordance with § 343.60(b)(2).

(2) *Analgesic-antipyretic and cough-cold combinations.* See § 341.40 of this chapter.

(3) *Aspirin and antacid combinations.* Aspirin identified in § 343.10(b)(1) may be combined with any antacid ingredient identified in § 331.11 of this chapter or any combination of antacids permitted in accordance with § 331.10(a) of this chapter provided that the finished product meets the requirements of § 331.10 of this chapter, is marketed in a form intended for ingestion as a solution, and bears labeling indications in accordance with § 343.60(b)(4).

(4) *Analgesic and diuretic combinations.* Any analgesic identified in § 343.10 or any combination of analgesics identified in § 343.20(a) may be combined with any diuretic identified in § 357.1012 of this chapter provided the product bears labeling indications in accordance with § 357.1060(b) of this chapter.

**Subpart C—Labeling**

**§ 343.50 Labeling of analgesic-antipyretic drug products.**

(a) *Statement of identity.* The labeling of the product contains the established name of the drug, if any, and identifies the product as a "pain reliever" or "analgesic (pain reliever)." If the product is also labeled to include the indication "to reduce fever," then the statement of identity of the product consists of the established name of the drug, if any, and identifies the product as a "pain reliever-fever reducer" or "analgesic (pain reliever)-antipyretic (fever reducer)."

(b) *Indications.* The labeling of the product states, under the heading "Indications," any of the phrases listed in this paragraph, as appropriate. Other truthful and nonmisleading statements, describing only the indications for use that have been established in this paragraph (b), may also be used, as provided in § 330.1(c)(2) of this chapter, subject to the provisions of section 502 of the act relating to misbranding and the prohibition in section 301(d) of the act against the introduction or delivery for introduction into interstate commerce of unapproved new drugs in violation of section 505(a) of the act.

(1) *For products containing any ingredient identified in § 343.10.* "For the temporary relief of minor aches and pains" [which may be followed by one or more of the following: ("associated with" (select one or more of the following: "a cold," "the common cold," "sore throat," "headache," "toothache," "muscular aches," "backache," "the premenstrual and menstrual periods" (which may be followed by: "(dysmenorrhea)," or "premenstrual and menstrual cramps" (which may be followed by: "(dysmenorrhea)))"), ("and for the minor pain from arthritis"), and ("and to reduce fever."))]

(2) *For products labeled only for children 2 years to under 12 years of age.* "For the temporary relief of minor aches and pains" [which may be followed by: ("associated with" (select one or more of the following: "a cold," "the common cold," "sore throat," "headache," or "toothache")) and/or ("and to reduce fever.")]

(3) *For products containing acetaminophen as identified in § 343.10(a).* The term "flu" may be added to the indications identified in paragraphs (b) (1) and (2) above.

(4) *Other required statements—(i) For products labeled only for children 2 to under 12 years of age containing any ingredient identified in § 343.10.* (A) The labeling of the product contains, on the principal display panel, either of the following:

(1) "Children's (trade name of product or generic name of ingredient(s))."

(2) "(Trade name of product or generic name of ingredient(s)) for Children."

(B) The labeling for adults in § 343.50(d) and the statement "Children 2 to under 12 years of age" in § 343.50(d)(3)(ii) are not required.

(ii) *For products labeled only for adults containing any ingredient identified in § 343.10 and any combination identified in § 343.20.* (A) The labeling of the product contains, on the principal display panel, either of the following:

(1) "Adult's (trade name of product or generic name of ingredient(s))."

(2) "(Trade name of product or generic name of ingredient(s)) for adults."

(B) The labeling for children in § 343.50(d) and the word "Adults" in § 343.50(d)(3)(i) are not required.

(C) The product should not contain any labeling for children under 12 years of age except the following statement under the heading "Directions," "Children under 12 years of age: consult a doctor."

(c) *Warnings.* The labeling of the product contains the following statements under the heading "Warnings." If applicable, warnings may be combined to eliminate duplicative words or phrases so the resulting warning(s) are clear and understandable.

(1) *For products labeled for adults—(i) For products containing any ingredient in § 343.10.* "Do not take this product for pain for more than 10 days or for fever for more than 3 days unless directed by a doctor. If pain or fever persists or gets worse, if new symptoms occur, or if redness or swelling is present, consult a doctor because these could be signs of a serious condition."

(ii) *For products containing any ingredient in § 343.10 and labeled for the relief of sore throat pain.* "If sore throat is severe, persists for more than 2 days, is accompanied or followed by fever, headache, rash, nausea, or vomiting, consult a doctor promptly."

(iii) *For products containing acetaminophen identified in § 343.10(a).* The following statement must follow the general warning identified in § 330.1(g)

of this chapter: "Prompt medical attention is critical for adults as well as for children even if you do not notice any signs or symptoms."

(iv) *For products containing aspirin or carbaspirin calcium identified in §§ 343.10 (b) and (c).* (A) "Do not take this product if you are allergic to aspirin or if you have asthma unless directed by a doctor."

(B) The following warning must follow the general warning identified in § 201.63(a) of this chapter:

"IMPORTANT: Do not take this product during the last 3 months of pregnancy unless directed by a doctor. Aspirin taken near the time of delivery may cause bleeding problems in both mother and child."

(C) *For products in a chewable dosage form.* "Do not take this product for at least 7 days after tonsillectomy or oral surgery unless directed by a doctor."

(v) *For products containing aspirin, carbaspirin calcium, choline salicylate, magnesium salicylate, or sodium salicylate identified in §§ 343.10 (b), (c), (d), (e), and (f).* (A) "If ringing in the ears or a loss of hearing occurs, consult a doctor before taking any more of this product."

(B) "Do not take this product if you have stomach problems (such as heartburn, upset stomach, or stomach pain) that persist or recur, or if you have ulcers or bleeding problems, unless directed by a doctor."

(C) *"Drug Interaction Precaution.* Do not take this product if you are taking a prescription drug for anticoagulation (thinning the blood), diabetes, gout, or arthritis unless directed by a doctor."

(vi) *For products containing choline salicylate, magnesium salicylate, or sodium salicylate identified in § 343.10 (d), (e), and (f).* "Do not take this product if you are allergic to salicylates (including aspirin) unless directed by a doctor."

(vii) *For products containing magnesium salicylate identified in § 343.10(e) in an amount more than 50 milliequivalents of magnesium in the recommended daily dosage.* "Do not take this product if you have kidney disease unless directed by a doctor."

(viii) *For products containing sodium salicylate identified in § 343.10(f)—(A) For products containing 0.2 milliequivalent (5 milligrams) or higher of sodium per dosage unit.* The labeling of the product contains the sodium content per dosage unit (e.g., tablet, teaspoonful) if it is 0.2 milliequivalent (5 milligrams) or higher.

(B) *For products containing more than 5 milliequivalents (125 milligrams) sodium in the maximum recommended daily dosage.* "Do not take this product

if you are on a sodium restricted diet unless directed by a doctor."

(2) *For products labeled for children 2 years to under 12 years of age—(i) For products containing any ingredient in § 343.10.* "Do not give this product for pain for more than 5 days or for fever for more than 3 days unless directed by a doctor. If pain or fever persists or gets worse, if new symptoms occur, or if redness or swelling is present, consult a doctor because these could be signs of a serious condition."

(ii) *For products containing any ingredient in § 343.10 and labeled for the relief of sore throat pain.* "If sore throat is severe, persists for more than 2 days, is accompanied or followed by fever, headache, rash, nausea, or vomiting, consult a doctor promptly."

(iii) *For products containing acetaminophen identified in § 343.10(a).* The following statement must follow the general warning identified in § 330.1(g) of this chapter: "Prompt medical attention is critical even if you do not notice any signs or symptoms."

(iv) *For products containing aspirin or carbaspirin calcium identified in § 343.10 (b) and (c).* (A) "Do not give this product to children who are allergic to aspirin or who have asthma unless directed by a doctor."

(B) *For products in a chewable dosage form.* "Do not give this product for at least 7 days after tonsillectomy or oral surgery unless directed by a doctor."

(v) *For products containing aspirin, carbaspirin calcium, choline salicylate, magnesium salicylate, or sodium salicylate identified in § 343.10 (b), (c), (d), (e), and (f).* (A) "If ringing in the ears or a loss of hearing occurs, consult a doctor before giving any more of this product."

(B) "Do not give this product to children who have stomach problems (such as heartburn, upset stomach, or stomach pain) that persist or recur, or who have ulcers or bleeding problems, unless directed by a doctor."

(C) *"Drug Interaction Precaution.* Do not give this product to children who are taking a prescription drug for anticoagulation (thinning the blood), diabetes, gout, or arthritis unless directed by a doctor."

(vi) *For products containing choline salicylate, magnesium salicylate, or sodium salicylate identified in § 343.10 (d), (e), and (f).* "Do not give this product to children who are allergic to salicylates (including aspirin) unless directed by a doctor."

(vii) *For products containing magnesium salicylate identified in § 343.10(e) in an amount more than 50 milliequivalents of magnesium in the*

recommended daily dosage. "Do not give this product to children who have kidney disease unless directed by a doctor."

(viii) For products containing sodium salicylate identified in § 343.10(f)—(A) For products containing 0.2 milliequivalent (5 milligrams) or higher of sodium per dosage unit. The labeling of the product contains the sodium content per dosage unit (e.g., tablet, teaspoonful) if it is 0.2 milliequivalent (5 milligrams) or higher.

(B) For products containing more than 5 milliequivalents (125 milligrams) sodium in the maximum recommended daily dosage. "Do not give this product to children who are on a sodium restricted diet unless directed by a doctor."

(3) For products labeled both for adults and for children 2 years to under 12 years of age. The labeling of the product contains the warnings identified in § 343.50(c)(1) except that the warning in § 343.50(c)(1)(i) is replaced with the following: "Do not take this product for pain for more than 10 days (for adults) or 5 days (for children), and do not take for fever for more than 3 days unless directed by a doctor. If pain or fever persists or gets worse, if new symptoms occur, or if redness or swelling is present, consult a doctor because these could be signs of a serious condition. Do not give this product to children for the pain of arthritis unless directed by a doctor."

(d) Directions. The labeling of the product contains the following statements under the heading "Directions."

(1) "For products labeled only for children 2 years to under 12 years of age." The dosage information for children in paragraphs (d) (2), (4), (5), and (6) of this section should be converted to directions that are easily understood by the consumer. For example, the number of 80-milligram, or 81-milligram, or 325-milligram dosage units corresponding to the children's doses in paragraph (d)(2) of this section can be expressed in the labeling as follows:

DIRECTIONS

Age (years)	Number of 80-mg or 81-mg <sup>1</sup> dosage units	Number of 325-mg <sup>1</sup> dosage units
Under 2	Consult a doctor.	
2 to under 4	2	1/2.
4 to under 6	3	3/4.
6 to under 9	4	1.
9 to under 11	4 to 5	1 to 1 1/4.

DIRECTIONS—Continued

Age (years)	Number of 80-mg or 81-mg <sup>1</sup> dosage units	Number of 325-mg <sup>1</sup> dosage units
11 to under 12	4 to 6	1 to 1 1/2.

<sup>1</sup> Dose may be repeated every 4 hours while symptoms persist, up to four times a day or as directed by a doctor.

(2) For products containing acetaminophen, aspirin, or sodium salicylate identified in § 343.10(a), (b), and (f). Adults: Oral dosage is 325 to 650 milligrams every 4 hours or 325 to 500 milligrams every 3 hours or 650 to 1,000 milligrams every 6 hours, while symptoms persist, not to exceed 4,000 milligrams in 24 hours, or as directed by a doctor. Children 11 to under 12 years of age: Oral dosage is 320 to 487.5 milligrams every 4 hours while symptoms persist, not to exceed 5 doses or 2,437.5 milligrams in 24 hours. Children 9 to under 11 years of age: Oral dosage is 320 to 406.3 milligrams every 4 hours while symptoms persist, not to exceed 5 doses or 2,031.5 milligrams in 24 hours. Children 6 to under 9 years of age: Oral dosage is 320 to 325 milligrams every 4 hours while symptoms persist, not to exceed 5 doses or 1,625 milligrams in 24 hours. Children 4 to under 6 years of age: Oral dosage is 240 to 243.8 milligrams every 4 hours while symptoms persist, not to exceed 5 doses or 1,219 milligrams in 24 hours. Children 2 to under 4 years of age: Oral dosage is 160 to 162.5 milligrams every 4 hours while symptoms persist, not to exceed 5 doses or 812.5 milligrams in 24 hours. Children under 2 years: Consult a doctor. The dosage schedules above are followed by "or as directed by a doctor."

(3) For products containing aspirin, carbaspirin calcium, choline salicylate, magnesium salicylate, or sodium salicylate identified in § 343.10(b), (c), (d), (e), and (f) intended for oral administration as a solid dosage form. (i) "Adults: Drink a full glass of water with each dose."

(ii) "Children 2 to under 12 years of age: Drink water with each dose."

(4) For products containing carbaspirin calcium identified in § 343.10(c). Adults: Oral dosage is 414 to 828 milligrams every 4 hours or 414 to 637 milligrams every 3 hours or 828 to 1,274 milligrams every 6 hours, while symptoms persist, not to exceed 5,096 milligrams in 24 hours. Children 11 to under 12 years of age: Oral dosage is 408.8 to 621 milligrams every 4 hours while symptoms persist, not to exceed 5 doses or 3,105 milligrams in 24 hours.

Children 9 to under 11 years of age: Oral dosage is 408.8 to 517.5 milligrams every 4 hours while symptoms persist, not to exceed 5 doses or 2,587.5 milligrams in 24 hours. Children 6 to under 9 years of age: Oral dosage is 408.8 milligrams every 4 hours while symptoms persist, not to exceed 5 doses or 2,070 milligrams in 24 hours. Children 4 to under 6 years of age: Oral dosage is 306.6 milligrams every 4 hours while symptoms persist, not to exceed 5 doses or 1,552.5 milligrams in 24 hours. Children 2 to under 4 years of age: Oral dosage is 204.4 milligrams every 4 hours while symptoms persist, not to exceed 5 doses or 1,035 milligrams in 24 hours. Children under 2 years: Consult a doctor. The dosage schedule above is followed by "or as directed by a doctor."

(5) For products containing choline salicylate identified in § 343.10(d). Adults: Oral dosage is 435 to 870 milligrams every 4 hours or 435 to 669 milligrams every 3 hours or 870 to 1,338 milligrams every 6 hours, while symptoms persist, not to exceed 5,352 milligrams in 24 hours. Children 11 to under 12 years of age: Oral dosage is 430 to 652.5 milligrams every 4 hours while symptoms persist, not to exceed 5 doses or 3,262.5 milligrams in 24 hours. Children 9 to under 11 years of age: Oral dosage is 430 to 543.8 milligrams every 4 hours while symptoms persist, not to exceed 5 doses or 2,719 milligrams in 24 hours. Children 6 to under 9 years of age: Oral dosage is 430 milligrams every 4 hours while symptoms persist, not to exceed 5 doses or 2,175 milligrams in 24 hours. Children 4 to under 6 years of age: Oral dosage is 322.5 milligrams every 4 hours while symptoms persist, not to exceed 5 doses or 1,632.5 milligrams in 24 hours. Children 2 to under 4 years of age: Oral dosage is 215 milligrams every 4 hours while symptoms persist, not to exceed 5 doses or 1,087.5 milligrams in 24 hours. Children under 2 years: Consult a doctor. The dosage schedule above is followed by "or as directed by a doctor."

(6) For products containing magnesium salicylate identified in § 343.10(e). Dosages are based on the tetrahydrate form of magnesium salicylate. Adults: Oral dosage is 377 to 754 milligrams every 4 hours or 377 to 580 milligrams every 3 hours or 754 to 1,160 milligrams every 6 hours, while symptoms persist, not to exceed 4,640 milligrams in 24 hours. Children 11 to under 12 years of age: Oral dosage is 372.4 to 65.5 milligrams every 4 hours while symptoms persist, not to exceed 5 doses or 2,827.5 milligrams in 24 hours. Children 9 to under 11 years of age: Oral

dosage is 372.4 to 471.3 milligrams every 4 hours while symptoms persist, not to exceed 5 doses or 2,356.5 milligrams in 24 hours. Children 6 to under 9 years of age: Oral dosage is 372.4 milligrams every 4 hours while symptoms persist, not to exceed 5 doses or 1,885 milligrams in 24 hours. Children 4 to under 6 years of age: Oral dosage is 279.3 milligrams every 4 hours while symptoms persist, not to exceed 5 doses or 1,414 milligrams in 24 hours. Children 2 to under 4 years of age: Oral dosage is 186.2 milligrams every 4 hours while symptoms exist, not to exceed 5 doses or 942.5 milligrams in 24 hours. Children under 2 years of age: Consult a doctor. The dosage schedule above is followed by "or as directed by a doctor."

(e) The word "physician" may be substituted for the word "doctor" in any of the labeling statements in this section.

(f) *Optional statement. For products containing aspirin, carbaspirin calcium, choline salicylate, magnesium salicylate, or sodium salicylate identified in § 343.10 (b), (c), (d), (e), and (f).* The labeling may state in a prominent place the following statement: "See your doctor for other uses of" [insert name of ingredient or trade name of product], but do not use for more than 10 days without consulting your doctor because serious side effects may occur."

#### § 343.60 Labeling of permitted combinations of active ingredients.

Statements of identity, indications, warnings, and directions for use, respectively, applicable to each ingredient in the product may be combined to eliminate duplicative words or phrases so that the resulting information is clear and understandable.

(a) *Statement of identity.* For a combination drug product that has an established name, the labeling of the product states the established name of the combination drug product, followed by the statement of identity for each ingredient in the combination, as established in the statement of identity sections of the applicable OTC drug monographs. For a combination drug product that does not have an established name, the labeling of the product states the statement of identity for each ingredient in the combination, as established in the statement of identity sections of the applicable OTC drug monographs.

(b) *Indications.* The labeling of the product states, under the heading "Indications," the indication(s) for each ingredient in the combination, as established in the indications sections of the applicable OTC drug monographs,

unless otherwise stated in this paragraph (b). Other truthful and nonmisleading statements, describing only the indications for use that have been established and listed in this paragraph may also be used, as provided in § 330.1(c)(2) of this chapter, subject to the provisions of section 502 of the act relating to misbranding and the prohibition in section 301(d) of the act against the introduction or delivery for introduction into interstate commerce of unapproved new drugs in violation of section 505(a) of the act.

(1) *For permitted combinations identified in § 343.20(a).* The indications in § 343.50(b)(1) should be used.

(2) *For permitted combinations identified in § 343.20(b)(1).* The indications are the following: "For the temporary relief of minor aches and pains with" (select one or more of the following: "heartburn," "sour stomach," or "acid indigestion") (which may be followed by: "and upset stomach associated with" (select one of the following, as appropriate: "this symptom" or "these symptoms."))

(3) *For permitted combinations identified in § 343.20(b)(2).* The indications in § 341.85 of this chapter should be used.

(4) *For permitted combinations identified in § 343.20(b)(3).* The indications are the following: "For the temporary relief of minor aches and pains with" (select one or more of the following: "heartburn," "sour stomach," or "acid indigestion") [which may be followed by: "and upset stomach associated with" (select one of the following, as appropriate: "this symptom" or "these symptoms"))] and "Also may be used for the temporary relief of minor aches and pains alone" [which may be followed by one or more of the following: ("such as associated with" (select one or more of the following: "a cold," "common cold," "sore throat," "headache," "toothache," "muscular aches," "backache," "the premenstrual and menstrual periods" (which may be followed by: "(dysmenorrhea)" or "premenstrual and menstrual cramps" (which may be followed by: "(dysmenorrhea)"))), ("and for the minor pain from arthritis"), and ("and to reduce fever."))]

(5) *For permitted combinations identified in § 343.20(b)(4).* The indications in § 357.1050(b) of this chapter should be used.

(c) *Warnings.* The labeling of the product states, under the heading "Warnings," the warning(s) for each ingredient in the combination, as established in the warnings sections of the applicable OTC drug monographs.

(d) *Directions.* The labeling of the product states, under the heading "Directions," directions that conform to the directions established for each ingredient in the directions sections of the applicable OTC drug monographs, unless otherwise stated in this paragraph (d). When the time intervals or age limitations for administration of the individual ingredients differ, the directions for the combination product may not exceed any maximum dosage limits established for the individual ingredients in the applicable OTC drug monograph.

(1) *For products containing permitted combinations identified in § 343.20(a)—*  
(i) *When each ingredient is present in the minimum allowable amount.* Adults: Oral dosage is every 4 hours while symptoms persist, not to exceed 6 doses in 24 hours or as directed by a doctor. Children under 12 years of age: Consult a doctor.

(ii) *When either ingredient is present in an amount above the minimum allowable quantity.* Adults: Oral dosage is every 6 hours while symptoms persist, not to exceed 4 doses in 24 hours or as directed by a doctor. Children under 12 years of age: Consult a doctor.

(e) *Optional labeling statements for permitted combinations identified in § 343.20(b)(3).* The labeling may state "Contains buffering ingredients." The labeling may also contain the statement in § 343.50(f).

#### § 343.80 Professional labeling.

The labeling of a product provided to health professionals (but not to the general public) may contain the following statements:

(a) *For products containing aspirin, carbaspirin calcium, choline salicylate, magnesium salicylate, or sodium salicylate identified in § 343.10 (b), (c), (d), (e), and (f) except those buffered with sodium.* "For rheumatoid arthritis, juvenile rheumatoid arthritis, systemic lupus erythematosus, osteoarthritis (degenerative joint disease), ankylosing spondylitis, psoriatic arthritis, Reiter's syndrome, and fibrositis."

(b) *For products containing aspirin identified in § 343.10(b) except those buffered with sodium.* The labeling states, under the heading "ASPIRIN FOR TRANSIENT ISCHEMIC ATTACKS," the following:

#### "Indication:

For reducing the risk of recurrent transient ischemic attacks (TIA's) or stroke in men who have had transient ischemia of the brain due to fibrin platelet emboli. There is inadequate evidence that aspirin or buffered aspirin is effective in reducing TIA's in women at the recommended dosage. There is

no evidence that aspirin or buffered aspirin is of benefit in the treatment of completed strokes in men or women.

#### Clinical Trials:

The indication is supported by the results of a Canadian study (1) in which 585 patients with threatened stroke were followed in a randomized clinical trial for an average of 28 months to determine whether aspirin or sulfipyrazone, singly or in combination, was superior to placebo in preventing transient ischemic attacks, stroke, or death. The study showed that, although sulfipyrazone had no statistically significant effect, aspirin reduced the risk of continuing transient ischemic attacks, stroke, or death by 19 percent and reduced the risk of stroke or death by 31 percent. Another aspirin study carried out in the United States with 178 patients, showed a statistically significant number of "favorable outcomes," including reduced transient ischemic attacks, stroke, and death (2).

#### Precautions:

Patients presenting with signs and symptoms of TIA's should have a complete medical and neurologic evaluation. Consideration should be given to other disorders that resemble TIA's. Attention should be given to risk factors: It is important to evaluate and treat, if appropriate, other diseases associated with TIA's and stroke, such as hypertension and diabetes.

Concurrent administration of absorbable antacids at therapeutic doses may increase the clearance of salicylates in some individuals. The concurrent administration of nonabsorbable antacids may alter the rate of absorption of aspirin, thereby resulting in a decreased acetylsalicylic acid/salicylate ratio in plasma. The clinical significance of these decreases in available aspirin is unknown.

Aspirin at dosages of 1,000 milligrams per day has been associated with small increases in blood pressure, blood urea nitrogen, and serum uric acid levels. It is recommended that patients placed on long-term aspirin treatment be seen at regular intervals to assess changes in these measurements.

#### Adverse Reactions:

At dosages of 1,000 milligrams or higher of aspirin per day, gastrointestinal side effects include stomach pain, heartburn, nausea and/or vomiting, as well as increased rates of gross gastrointestinal bleeding."

(Other applicable warnings related to the use of aspirin as described in § 343.50(c) may also be included here.)

#### Dosage and Administration:

Adult oral dosage for men is 1,300 milligrams a day, in divided doses of 650 milligrams twice a day or 325 milligrams four times a day.

#### References

- (1) The Canadian Cooperative Study Group, "A Randomized Trial of Aspirin and Sulfipyrazone in Threatened Stroke," *New England Journal of Medicine*, 299:53-59, 1978.
- (2) Fields, W.S., et al., "Controlled Trial of Aspirin in Cerebral Ischemia" *Stroke* 8:301-316, 1977."

(c) For products containing aspirin identified in § 343.10(b) or permitted combinations identified in § 343.20(b)(3). The labeling states, under the heading "ASPIRIN FOR MYOCARDIAL INFARCTION," the following:

#### "Indication

Aspirin is indicated to reduce the risk of death and/or non-fatal myocardial infarction in patients with a previous infarction or unstable angina pectoris.

#### Clinical Trials

The indication is supported by the results of six large, randomized multicenter, placebo-controlled studies involving 10,816, predominantly male, post-myocardial infarction (MI) patients and one randomized placebo-controlled study of 1,266 men with unstable angina (1-7). Therapy with aspirin was begun at intervals after the onset of acute MI varying from less than 3 days to more than 5 years and continued for periods of from less than 1 year to 4 years. In the unstable angina study, treatment was started within 1 month after the onset of unstable angina and continued for 12 weeks, and patients with complicating conditions such as congestive heart failure were not included in the study.

Aspirin therapy in MI patients was associated with about a 20-percent reduction in the risk of subsequent death and/or non-fatal reinfarction, a median absolute decrease of 3 percent from the 12- to 22-percent event rates in the placebo groups. In aspirin-treated unstable angina patients the reduction in risk was about 50 percent, a reduction in the event rate of 5 percent from the 10-percent rate in the placebo group over the 12-weeks of the study.

Daily dosage of aspirin in the post-myocardial infarction studies was 300 milligrams in one study and 900 to 1,500 milligrams in 5 studies. A dose of 325 milligrams was used in the study of unstable angina.

#### Adverse Reactions

##### Gastrointestinal Reactions

Doses of 1,000 milligrams per day of aspirin caused gastrointestinal symptoms and bleeding that in some cases were clinically significant. In the largest post-infarction study (the Aspirin Myocardial Infarction Study (AMIS) with 4,500 people), the percentage incidences of gastrointestinal symptoms for the aspirin (1,000 milligrams of a standard, solid-tablet formulation) and placebo-treated subjects, respectively, were: stomach pain (14.5 percent; 4.4 percent); heartburn (11.9 percent; 4.8 percent); nausea and/or vomiting (7.8 percent; 2.1 percent); hospitalization for gastrointestinal disorder (4.8 percent; 3.5 percent). In the AMIS and other trials, aspirin-treated patients had increased rates of gross gastrointestinal bleeding. Symptoms and signs of gastrointestinal irritation were not significantly increased in subjects treated for unstable angina with buffered aspirin in solution."

(Other applicable warnings related to the use of aspirin as described in § 343.50(c) may also be included here.)

#### "Cardiovascular and Biochemical

In the AMIS trial, the dosage of 1,000 milligrams per day of aspirin was associated with small increases in systolic blood pressure (BP) (average 1.5 to 2.1 millimeters) and diastolic BP (0.5 to 0.8 millimeters), depending upon whether maximal or last available readings were used. Blood urea nitrogen and uric acid levels were also increased, but by less than 1.0 milligram percent.

Subjects with marked hypertension or renal insufficiency had been excluded from the trial so that the clinical importance of these observations for such subjects or for any subjects treated over more prolonged periods is not known. It is recommended that patients placed on long-term aspirin treatment, even at doses of 300 milligrams per day, be seen at regular intervals to assess changes in these measurements.

#### Sodium in Buffered Aspirin for Solution Formulations

One tablet daily of buffered aspirin in solution adds 553 milligrams of sodium to that in the diet and may not be tolerated by patients with active sodium-retaining states such as congestive heart or renal failure. This amount of sodium adds about 30 percent to the 70- to 80-milliequivalents intake suggested as appropriate for dietary treatment of essential hypertension in the "1984 Report of the Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure" (8).

#### Dosage and Administration

Although most of the studies used dosages exceeding 300 milligrams, 2 trials used only 300 milligrams and pharmacologic data indicate that this dose inhibits platelet function fully. Therefore, 300 milligrams or a conventional 325 milligram aspirin dose is a reasonable, routine dose that would minimize gastrointestinal adverse reactions. This use of aspirin applies to both solid, oral dosage forms (buffered and plain aspirin) and buffered aspirin in solution.

#### References

- (1) Elwood, P.C., et al., "A Randomized Controlled Trial of Acetylsalicylic Acid in the Secondary Prevention of Mortality from Myocardial Infarction," *British Medical Journal*, 1:436-440, 1974.
- (2) The Coronary Drug Project Research Group, "Aspirin in Coronary Heart Disease," *Journal of Chronic Diseases*, 29:625-642, 1976.
- (3) Breddin K., et al., "Secondary Prevention of Myocardial Infarction: A Comparison of Acetylsalicylic Acid, Phenprocoumon or Placebo," *Homeostasis*, 470:263-268, 1979.
- (4) Aspirin Myocardial Infarction Study Research Group, "A Randomized, Controlled Trial of Aspirin in Persons Recovered from Myocardial Infarction," *Journal of the American Medical Association*, 243:661-669, 1980.
- (5) Elwood, P.C., and P.M. Sweetnam, "Aspirin and Secondary Mortality after Myocardial Infarction," *Lancet*, II:1313-1315, December 22-29, 1979.

(6) The Persantine-Aspirin Reinfarction Study Research Group, "Persantine and Aspirin in Coronary Heart Disease," *Circulation*, 62:449-461, 1980.

(7) Lewis, H.D., et al., "Protective Effects of Aspirin Against Acute Myocardial Infarction and Death in Men with Unstable Angina, Results of a Veterans Administration Cooperative Study," *New England Journal of Medicine*, 309:396-403, 1983.

(8) "1984 Report of the Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure," United States Department of Health and Human Services and United States Public Health Service, National Institutes of Health, Publication No. NIH 84-1088, 1984."

#### Subpart D—Testing Procedures

##### § 343.90 Dissolution Testing.

(a) *Acetaminophen and aspirin tablets*. Acetaminophen and aspirin tablets must meet the dissolution standard for acetaminophen and aspirin tablets as contained in U.S.P. XXI at page 14.

(b) *Aspirin capsules*. Aspirin capsules must meet the dissolution standard for aspirin capsules as contained in U.S.P. XXI at page 77.

(c) *Aspirin delayed-release capsules and aspirin delayed-release tablets*.

Aspirin delayed-release capsules and aspirin delayed-release tablets must meet the dissolution standard for aspirin delayed-release capsules and aspirin delayed-release tablets as contained in U.S.P. XXI Supplement 3 at pages 1972 and 1973, respectively.

(d) *Aspirin tablets*. Aspirin tablets must meet the dissolution standard for aspirin tablets as contained in U.S.P. XXI Supplement 4 at page 2130.

(e) *Aspirin, alumina, and magnesia tablets*. Aspirin in combination with alumina and magnesia in a tablet dosage form must meet the dissolution standard for aspirin, alumina, and magnesia tablets as contained in U.S.P. XXI Supplement 2 at pages 1812 and 1813.

(f) *Buffered aspirin tablets*. Buffered aspirin tablets must meet the dissolution standard for buffered aspirin tablets as contained in U.S.P. XXI Supplement 4 at page 2131.

#### PART 369—INTERPRETATIVE STATEMENTS RE WARNINGS ON DRUGS AND DEVICES FOR OVER-THE-COUNTER SALE

4. The authority citation for 21 CFR Part 369 continues to read as follows:

Authority: Secs. 502, 503, 506, 507, 701, 52 Stat. 1050-1052 as amended, 1055-1056 as amended, 55 Stat. 851, 59 Stat. 463 as amended (21 U.S.C. 352, 353, 356, 357, 371); 21 CFR 5.10 and 5.11.

##### § 369.20 [Amended]

5. In Subpart B, § 369.20 *Drugs; recommended warning and caution statements* is amended by removing the entry for "SALICYLATES, INCLUDING ASPIRIN AND SALICYLAMIDE (EXCEPT METHYL SALICYLATE, EFFERVESCENT SALICYLATE PREPARATIONS, AND PREPARATIONS OF AMINOSALICYLIC ACID AND ITS SALTS)."

##### § 369.21 [Amended]

6. In Subpart B, § 369.21 *Drugs; warning and caution statements required by regulations* is amended by removing the entry for "ACETAMINOPHEN (N-ACETYL-*p*-AMINOPHENOL)."

Dated: August 5, 1988.

Frank E. Young,

Commissioner of Food and Drugs.

[FR Doc. 88-26157 Filed 11-15-88; 8:45 am]

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