DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 201

[Docket No. 90N-0169]

RIN 0905-AA06

Labeling for Oral and Rectal Over-the-Counter Aspirin and Aspirin-Containing Drug Products; Final Rule

AGENCY: Food and Drug Administration.

ACTION: Final rule.

SUMMARY: The Food and Drug Administration (FDA) is amending its regulations to require that the labeling of oral and rectal over-the-counter (OTC) aspirin and aspirin-containing drug products for human use bear a warning that such products should not be used during the last 3 months of pregnancy unless directed by a doctor. FDA is issuing this final rule after considering the report and recommendations of the Advisory Review Panel on OTC Internal Analgesic and Antirheumatic Drug Products, public comments on the agency's proposed regulation for these OTC drug products, which was issued in the form of a tentative final monograph, and all new data and information that have come to the agency's attention. FDA is taking this action in order to alert pregnant women that aspirin or aspirin-containing drug products taken without medical supervision during the last 3 months of pregnancy may cause problems in the unborn child or complications during delivery.

EFFECTIVE DATE: August 6, 1990. Manufacturers of affected drug products initially introduced or initially delivered for introduction into interstate commerce will have until July 5, 1991 to comply with the labeling requirement set forth in 21 CFR 201.63(e).

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SUPPLEMENTARY INFORMATION:

I. Background

In the **Federal Register** of July 8, 1977 (42 FR 35346), FDA published, under § 330.10(a)(6) (21 CFR 330.10(a)(6)), an advance notice of proposed rulemaking to establish a monograph for OTC internal analgesic, antipyretic, and antirheumatic drug products, together with the recommendations of the Advisory Review Panel on OTC Internal Analgesic and Antirheumatic Drug Products (Internal Analgesic Panel), which was the advisory review panel responsible for evaluating data on the active ingredients in these drug classes. One of the Panel's recommendations was that OTC drug products containing aspirin and carbaspirin calcium bear the following warning: "Do not take this product during the last three months of pregnancy except under the advice and supervision of a physician." This recommendation was based on the Panel's evaluation of data that led it to conclude that acute aspirin use during pregnancy could prolong the duration of labor, increase maternal blood loss both before and after delivery, and cause a change in the hemostatic mechanisms of the newborn child (42 FR 35348 at 35402). For these reasons, the Panel concluded that the acute use of aspirin during the third trimester of pregnancy poses a potential hazard and the above-cited warning should appear on all OTC aspirin-containing drug products (42 FR 35346 at 35405). Interested persons were invited to file comments by December 5, 1977. Reply comments in response to the comments filed in the initial comment period could be filed by February 6, 1978.

In accordance with § 330.10(a)(10) the data and information considered by the Panel were put on public display in the Dockets Management Branch (HFA-305), Food and Drug Administration, Rm. 4-62, 5600 Fishers Lane, Rockville, MD 20857, after deletion of a small amount of trade secret information.

In response to the advance notice of proposed rulemaking for OTC internal analgesic, antipyretic, and antirheumatic drug products, two trade associations, several drug manufacturers, many health professionals, several consumers, a drug standard-setting association, two health professional associations, a health foundation, and one consumer group submitted comments. However, none of these comments discussed the Panel's proposed warning against the use of aspirin-containing products in the third trimester of pregnancy.

The agency's proposed regulation, in the form of a tentative final rule, for OTC internal, antipyretic, and antirheumatic drug products was published in the **Federal Register** of November 16, 1988 (53 FR 46204). As part of its proposed regulation, the agency expanded the Panel's proposed warning concerning the use of aspirin-containing products during the last 3 months of pregnancy in order to inform consumers of the reason for the warning, as follows: "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" (53 FR 46253). This warning appeared in § 343.50(c)(1)(iv)(B) of the tentative final monograph. The agency further proposed that the warning follow the general pregnancy warning in § 201.63 that is required for all OTC drugs that are intended for systemic absorption, which includes oral and rectal aspirin and aspirin-containing drug products. Interested persons were invited to file by May 16, 1989, written comments, or objections, or requests for oral hearing before the Commissioner of Food and Drugs regarding the proposal. Interested persons were invited to file comments on the agency's economic impact determination by May 16, 1989. New data could have been submitted until November 16, 1989, and comments on the new data until January 16, 1990.

In a notice published in the **Federal Register** of January 16, 1990 (55 FR 1471), the agency advised that it was extending to March 16, 1990, the period for comments on new data for the notice of proposed rulemaking for OTC internal analgesic, antipyretic, and antirheumatic drug products.

Five manufacturers, two trade associations, and one consumer submitted comments on the proposed third trimester pregnancy warning for OTC aspirin-containing drug products. There was one request for a hearing. Copies of the comments and the hearing request are on public display in the Dockets Management Branch. Additional information that has come to the agency's attention since publication of the proposed rule is also on public display in the Dockets Management Branch. In proceeding with this final rule, the agency has considered all comments, new data, and the request for an oral hearing related to this issue.

II. Highlights of the Final Rule

This final rule requires a new warning statement for all OTC oral and rectal aspirin and aspirin-containing drug products. This new warning statement must appear in boldface type and all capital letters and immediately follow the general pregnancy-nursing warning statement required by § 201.63, under the heading "Warinings," as follows:

As with any drug, if you are pregnant or nursing a baby, seek the advice of a health professional before using this product. IT IS ESPECIALLY IMPORTANT NOT TO USE" (select "ASPIRIN" or " CARBASPIRIN CALCIUM," as appropriate) "DURING THE LAST 3 MONTHS OF PREGNANCY UNLESS SPECIFICALLY DIRECTED TO DO SO BY A DOCTOR BECAUSE IT MAY CAUSE PROBLEMS IN THE UNBORN CHILD OR COMPLICATIONS DURING DELIVERY."

The agency has determined that this new warning statement concerning use during the last 3 months of pregnancy should appear in the labeling of OTC aspirin and aspirin-containing drug products prior to finalization of the monograph for OTC internal analgesic, antipyretic, and antirheumatic drug products in order to alert pregnant women of the additional conditions under which these OTC drug products should not be used without medical supervision. The agency notes that similar warnings have been approved in new drug applications for OTC ibuprofen-containing drug products (an OTC analgesic similar to aspirin) for more than 5 years.

III. Summary of the Comments

The agency received 10 comments on its proposed third trimester warning for aspirin and aspirin-containing drug products. One comment endorsed the agency's proposed warning, which was as follows: "IMPORTANT: Do not take this product during the last three months of pregnancy unless directed by a doctor. Aspirin when taken near the time of delivery may cause bleeding problems in both mother and child." Several comments, including one from a trade association, recommended that the agency's proposed warning be deleted. Several of the comments contended that the warning, when used in conjunction with the general pregnancy warning required by § 201.63 ("As with any drug, if you are pregnant or nursing a baby, seek the advice of a health professional before using this product.") may confuse and unduly frighten consumers.

One comment noted that the Panel's recommendation in 1977 for an aspirin pregnancy warning was made before the agency implemented its requirement in 1982 for a general pregnancy-nursing warning for all drugs intended for systemic absorption. Other comments contended that the agency's proposed warning is unnecessary and that the general pregnancy warning is adequate to inform pregnant consumers of the need to consult a trained health professional prior to using OTC drug products containing aspirin. Another comment argued that the two warnings taken together would reduce the likelihood that consumers will follow the directions of the general warning to consult a doctor before use of these products during the first six months of pregnancy. The comment concluded that the agency's proposed warning could result in the inappropriate use of OTC aspirin drug products during pregnancy.

Another comment stated that the warning could cause consumer confusion. The comment asserted that the first sentence of the proposed warning could lead consumers to believe that there may be circumstances in which a woman in the third trimester of pregnancy should take aspirin when directed to do so by a doctor, while the second portion of the proposed warning clearly says that the use of aspirin near the time of delivery may cause bleeding problems in both mother and child. Another comment argued that the agency's proposed warning could lead a consumer to assume that aspirin taken prior to the last trimester is completely without risk. The comment stated its belief that the explicit speculation included in the proposed warning goes beyond responsible regulation and that it may frighten consumers who have been prescribed aspirin during pregnancy for legitimate medical needs.

One comment warned that the proliferation of warnings proposed for inclusion in the labeling of these OTC drug products carries with it the risk that the effectiveness of the warnings may be diluted, so that truly significant warnings will be overlooked by consumers. The comment recommended use of a single warning instead of several specific warnings dealing with the same subject. Citing the agency's proposed third trimester pregnancy warning as an example, the comment suggested that the general pregnancy warning and the agency's proposed warning be combined, to read as follows: "As with any drug, if you are pregnant or nursing a baby, do not take unless directed by a doctor. This is particularly important for aspirin during the last 3 months of pregnancy since it may cause bleeding problems in mother or child." The comment contended that the combined warning would be more effective and requested a hearing if the agency disagrees with its position on this issue.

One comment questioned the need for the additional warning for two reasons: (1) Lack of evidence demonstrating the need for such a warning and (2) lack of evidence that the general pregnancy warning is ineffective in accomplishing the goal of the more specific proposed warning. The comment further questioned the need for the proposed warning based on two studies (Refs. 1 and 2) that suggest that low daily doses (60 or 100 milligrams (mg)) of aspirin taken during the third trimester of pregnancy may reduce the incidence of pregnancy-induced hypertension and preeclamptic toxemia in women at risk from these conditions. The comment cautioned that the agency's proposed warning may jeopardize a woman's compliance with this promising new use of aspirin and may therefore interfere with the physician-patient relationship.

Another comment submitted a study (Ref. 3) designed to assess whether there is an association between third trimester aspirin use and an increase in the incidence of stillbirths or in the degree of neonatal bleeding, maternal bleeding, length of gestation, or length of labor. Subsequently, the comment submitted another analysis of the same data base (Ref. 4), which assesses the effect of aspirin use in the last 10 days of pregnancy. The comment asserted that these data demonstrate that a third-trimester pregnancy warning for aspirin is not necessary.

Subsequently, the trade association, which had requested deletion of the proposed warning, noted the more recently submitted new scientific information (Refs. 3 and 4) and requested that the agency resolve the third-trimester pregnancy warning for OTC aspirin-containing drug products without awaiting resolution of the other issues presented in the tentative final monograph. Numerous legal precedents were cited to support its suggestion (Ref. 5). The comment added that FDA has finalized labeling regulations outside the OTC drug review monograph process, mentioning the general pregnancy-nursing warning in § 201.63. That warning applied to OTC aspirin-containing drug products, and other marketed OTC drugs, prior to issuance of a final monograph. The comment recommended that the agency publish expeditiously a final rule that would require, if appropriate, the following third-trimester pregnancy warning on the labeling of all OTC aspirin and aspirin-containing analgesic-antipyretic drug products: "Do not use this product during the last 3 months of pregnancy unless advised to do so by a doctor because it may cause problems during delivery." The comment contended that the language of its proposed warning is consistent with the third-trimester warning language that now appears on the OTC analgesic ibuprofen. The comment asserted that this warning is likely to receive nationwide acceptance and thereby maintain national uniformity in the labeling of aspirin and other OTC analgesics. The comment also recommended that the final rule provide that warnings may be combined to eliminate duplicative words or phrases so that the resulting warnings are clear and understandable, as proposed in the tentative final monograph.

IV. The Agency's Conclusions on the Comments

The agency has determined that the third-trimester pregnancy warning should be finalized before resolution of the other matters pending in the tentative final monograph for OTC internal analgesic, antipyretic, and antirheumatic drug products. The agency is finalizing this warning for OTC aspirin-containing drug products now, in order to ensure that consumers have adequate information concerning the use of these products during the third trimester of pregnancy. This will enable consumers to make intelligent and informed decisions concerning their safe use.

The agency does not agree with the comments that contend that the agency's proposed third-trimester pregnancy warning is unnecessary in light of the general pregnancy warning already required to appear on these OTC drug products. However, after reviewing the Panel's conclusions, the submitted comments, and the recently available data on this issue, the agency now believes that a specific reference to bleeding as proposed in the tentative final monograph (53 FR 46204 at 46253) is not necessary. Use of aspirin during the third trimester poses potential risks. Therefore, the agency believes that it is important that consumers be specially advised not to use aspirin and aspirin-containing OTC drug products during the third trimester of pregnancy unless directed to do so by a doctor.

In a recent study by Brent, Shook, and Wilson (Ref. 3), the outcomes of pregnancies in which aspirin was used during the third trimester of pregnancy were compared to the outcomes of pregnancies in which no aspirin was used. The study also evaluated the effect of different aspirin exposure levels during the third trimester and the last month of pregnancy. The data base used in this study was generated by the National Collaborative Perinatal Project (NCPP), sponsored by the National Institutes of Health. This data base resulted from a comprehensive multicenter study that monitored approximately 58,000 pregnancies and their outcomes during a 16-year period (1959–1974) in an effort to clarify the etiology of cerebral palsy and mental retardation. The study collected information from participating women on many factors that may have affected cerebral palsy and mental retardation such as other conditions, disease states, medications, treatments, education, socio-economic level, sex of the neonate, and others. This information was collected from participating women on an ongoing basis from the time they were diagnosed as pregnant and continuing through delivery. Information also was collected on the neonates from the time of delivery until age eight.

Subjects were included in the analysis by Brent, Shook, and Wilson when the NCPP data base contained a record of the outcome of the pregnancy and information indicating whether or not aspirin was used. Aspirin exposure was recorded as "low dose" (subject took aspirin on only 1 day in a lunar month), "medium dose" (subject took aspirin on 2 to 7 days in a lunar month), and "high dose" (subject took aspirin on more than 7 days in a lunar month). However, neither the total dose of aspirin taken on any given day nor the total number of days of aspirin use if over 8 days was reported.

The study evaluated five endpoints: incidence of stillbirths, degree of neonatal bleeding, maternal bleeding, length of gestation, and length of labor. Because neonatal bleeding was not directly recorded in the NCPP data base, data on neonatal intracranial bleeding, neonatal hematocrit, and neonatal hemoglobin (after 48 hours) were analyzed to give an estimate of the degree of neonatal bleeding. The authors stated that a reduction in hematocrit by 0.6 percent after 48 hours or a reduction in hemoglobin by 0.2 gram (g) indicated a blood loss of approximately 1 percent. Both stillbirth and neonatal intracranial bleeding were noted as either present or absent, while the other outcomes were measured on a continuous scale.

Other factors which when present during pregnancy may have influenced the above uncorrected risk estimates were identified from previous literature and tested for possible influence on study outcomes. The other factors analyzed for included 62 non-drug factors and 27 categories of drugs. Each of these covariables was tested to determine whether it was associated with the unadjusted risk of the investigated outcomes and whether it was associated with the use of aspirin in the study. The unadjusted risk assessments for the evaluated outcomes were then corrected for each of these covariables simultaneously and both unadjusted and adjusted results were reported.

Pregnancies in which the above outcomes were recorded were evaluated by comparing aspirin-exposed pregnancies to unexposed pregnancies. The proportions of women who demonstrated one of these outcomes and who were exposed to aspirin in one of three dosage groups during the last 3 months of pregnancy were compared to the proportions of women in the group with no aspirin exposure. The exposure groups were: (1) Any exposure to aspirin regardless of doses, (2) low-dose group, and (3) high-dose group. In addition to the evaluation of the effects of aspirin exposure during the third trimester of pregnancy, women exposed at the high and low dose during the last month of pregnancy were compared to women not exposed to any aspirin during that time.

There was no statistically significant association of neonatal intracranial bleeding with any level of aspirin use in the third trimester or in the last month of pregnancy. The authors considered the data for these associations sufficient to detect a difference as small as 1 percent between any of the aspirin-user groups and the unexposed population, with a power of 90 percent or greater.

The mean neonatal hemoglobin of 18.2 g percent for the unexposed group was not changed significantly for any level of aspirin exposure during either the third trimester or the last month of pregnancy. However, the low-dose exposure during the last month suggests a decrease in the mean hemoglobin level of 0.1 g percent, indicating less blood loss among the unexposed group. An adjustment of the data for the last month of pregnancy for covariables indicated that there is no significant difference between the two means when aspirin was considered independently. The authors considered the data for this outcome sufficient to detect a difference of 0.2 g percent between any of the aspirin-user groups and the exposed population, with a power of 90 percent.

The unadjusted third-trimester exposure data for the mean neonatal hematocrit indicated that the unexposed group had a significantly higher mean hematocrit (58.6 percent) than the exposed groups ($p < 0.001$). The results for the last-month exposure groups were essentially identical to those for the third-trimester exposure group. The data from both levels (low and high dose) indicate a small (less than 1 percent) but statistically signifcant decrease in the mean neonatal hematocrit. The authors reported that adjustment of the data for covariables removed the statistical significance of the difference for both exposure groups. The authors contend that the data for the 3-month exposure were sufficient to detect a difference of 0.3 percent hematocrit between any of the exposure groups and the unexposed group, with a power of 90 percent or greater.

With regard to maternal blood loss, the study reported that the mean loss of 226.2 milliliters (mL) of blood for the unexposed group was not significantly

different from any of the aspirin groups (< 5.1 mL) based on both the adjusted and unadjusted data. The data from the low- and high-dose exposures of aspirin during the last month of pregnancy also showed no statistically significant change in either the adjusted or unadjusted data. The authors point out that the maternal blood loss measurements for this study were based on delivery room estimates of the quantity of blood lost during delivery. The authors report that the data for this variable were sufficient to detect a difference of 8 mL of blood loss for the 3-month data and a 7-mL blood loss for the 1-month data between the unexposed and exposed populations, with a power of 90 percent or greater.

The study also attempted to ascertain whether or not there was a dose effect of aspirin over the third trimester of pregnancy by comparing subjects who were not exposed to aspirin to subjects with exposure to aspirin (1) Any time during the last trimester, (2) with low- and high-use aspirin exposure during the third trimester, and (3) with low- and high-use aspirin exposure during the last month.

The third-trimester low-dose aspirin exposure group included those subjects who ingested aspirin on only 1 day in the last month of pregnancy and during at least 1 other month of the last 3 lunar months of pregnancy. Where inclusion was based on a 2-month exposure, the remaining month had to have had no exposure. To qualify for the high-dose aspirin group, the subjects must have ingested aspirin on at least 8 days in the last month of pregnancy and during at least one more of the last 3 lunar months of pregnancy, with an intermediate exposure (2 to 6 days) in the month in which a high exposure was not recorded. The last-month low-use group included subjects whose aspirin ingestion was only 1 day during the last month. The high-use group included subjects that had ingested aspirin on at least 8 days during the last month. The authors reported that their analysis of data from the any-aspirin exposure group and the groups with high and low dose aspirin exposure during the third trimester and last month of pregnancy indicated no aspirin association for neonatal intracranial bleeding, neonatal hematocrit, and neonatal hemoglobin. Noting the fact that the data for maternal blood loss were not based on a precise quantitative measurement, which may affect the reliability of the results, the authors reported that there was no significant difference in maternal blood loss between the any-aspirin-exposure group and the unexposed group. The evaluation of the 3-month high- and low-dose groups, and the last month data, also indicated no difference.

In summary, the authors concluded that this extensive data base shows that the ingestion of aspirin in OTC doses during the last 3 months of pregnancy does not lead to a clinically relevant adverse result due to bleeding in any of the outcomes studied. According to the authors, the study indicated no increase in maternal bleeding or neonatal bleeding (as measured by either neonatal intracranial bleeding, neonatal hemoglobin, or neonatal hematocrit).

In a subsequent study (Ref. 4) of the same NCPP data base, the same authors examined the risks to mothers who were exposed to aspirin during the last 10 days before delivery. The study compared exposed mothers and their neonates (both premature and full-term infants) with those who were never exposed to aspirin during pregnancy. The study involved the analysis of three bleeding endpoints: neonatal intracranial bleeding, neonatal hemoglobin, and neonatal hematocrit. In addition, based on the assumption that there was no aspirin effect on these endpoints, a fourth indicator of possible intracranial bleeding at birth, the intelligence quotient (IQ) at 7 years of age, was analyzed.

Subjects were included in the study if their records indicated that they had used aspirin within the last 10 days before delivery or had not used aspirin at all during their pregnancy but had the outcome being evaluated. Premature infants were defined by a length of gestation of less than or equal to 33 weeks and a birthweight of less than 1,500 g. Full-term infants were defined as having a gestation period greater than or equal to 34 weeks and a birth weight equal to or greater than 1,500 g. The infants whose mothers were exposed to aspirin during the last 10 days of pregnancy were compared to infants born to mothers with no aspirin exposure during this same period. An analysis of maternal bleeding in the full-term population was also done. Detailed information regarding the number of tablets or capsules of aspirin-containing products that the subjects took was abstracted from information in the NCPP data base.

Neonatal intracranial bleeding was evaluated on the basis of the presence or absence of the condition. Neonatal hemoglobin, neonatal hematocrit, maternal bleeding, and IQ at 7 years were measured on a continuous scale. As in the study above, the data were analyzed for the effect of other factors which may have influenced the uncorrected risk estimates. However, the method of analysis used in this study differs from that of the previous study (Ref. 3) because only the effect of variables likely to have had an influence on the unadjusted results were analyzed for, rather than all 89 potential covariables.

For the outcome of neonatal intracranial bleeding in full-term infants, the study reported that there was no difference in the percentage of infants who experienced intracranial bleeding when a comparison between the exposed and unexposed groups was made. For the outcome of neonatal hemoglobin (after 48 hours), the aspirin-exposure group had a mean of 18.3 g percent, and the no aspirin-exposure group had a mean of 18.2 g percent. The difference between these two means was not statistically significant. The data from the aspirin-exposure and the no-aspirin-exposure groups indicated that the unadjusted mean hematocrit of the exposed infants (57.8 percent) was less than the value for the nonexposed infants (58.8 percent) and that the difference was statistically significant with a probability of 0.0001. The results showed on covariant analysis that aspirin exposure during the last 10 days of pregnancy had an opposite effect, i.e., it caused less effect on neonatal hematocrit than no aspirin exposure during this period. An assessment of the IQ at age 7 indicated a statistically significant increase ($p=0.0001$) in the IQ of infants at age 7 of the aspirin exposure group (98.0) over the unexposed group (96.1), but an adjustment of the data for the effects of covariables indicated no significant difference in IQ between the two groups.

Maternal bleeding was assessed in the same way it had been in the other study (Ref. 3). The authors stated that the analysis of these data was extremely difficult due to the large standard deviations and the skewed distributions of the blood loss which they attributed to the fact that the blood loss values were estimated and not measured. Comparison of the unadjusted means for the blood loss indicated the unexposed group lost 7.5 mL more blood than the exposed group. The difference was found to be statistically significant ($p = 0.002$). The authors reported that this result indicated that the use of aspirin during the last 10 days of pregnancy resulted in less blood loss at delivery; however, the difference of 7.5 mL (which is equivalent to 1½ teaspoons) is clinically insignificant.

A comparison of the incidence of neonatal intracranial bleeding in exposed and unexposed premature infants was not statistically significant (14.0 and 12.1 percent, respectively). The authors concluded that there is no significant increase in the risk of neonatal intracranial hemorrhage between the exposed and unexposed groups.

In the assessment of the data on premature neonatal hemoglobin (after 48 hours), the study indicated that the aspirin group showed significantly less neonatal hemoglobin than the no-aspirin-exposure group. However, when these results were adjusted for covariables that were deemed to have a significant effect on this outcome, there was no significant difference between the aspirin-exposure and no-exposure groups. The unadjusted mean hematocrit of the exposed infants was less than the value for the unexposed infants, but this difference was not statistically significant. When these results were corrected for covariables, the results also were not statistically significant. With regard to the assessment of IQ at 7 years, the study contained little data; and both the unadjusted and adjusted values indicated that there was no statistically significant difference.

The agency concludes that upon evaluation of all the available data, including the new uses discussed below, that aspirin used in the third trimester of pregnancy poses some potential risks, only one of which is bleeding. It is important to advise women in their third trimester of pregnancy to consult a doctor before using any OTC drug products containing aspirin or carbaspirin calcium. The agency continues to agree with the Panel and concludes that these products should bear a third-trimester pregnancy warning.

The Panel's conclusion that acute aspirin use during the third trimester of pregancy poses a potential risk for both mother and infant was based on its evaluation of data on the effects of aspirin on various aspects of pregnancy as extensively reported in the literature through 1977 (42 FR 35346 at 35399). In addition to its concerns about the changing of the hemostatic mechanisms in the newborn and increasing maternal blood loss, the Panel's discussion of the evaluated data regarding the effects of aspirin or carbaspirin calcuim on pregnancy also included other effects of these ingredients on pregnancy. Such other effects are due to multiple effects of prostaglandin inhibition on the fetus and on delivery.

The Panel noted that Tuchman-Duplessis et al. (Ref. 6) reported that the administration of 200 mg/kilogram (kg)/day of aspirin to rats during the last 6 days of pregnancy resulted in a prolongation of the duration of pregnancy, a prolongation of parturition, and appearance of dystocia (abnormal labor) in some animals, which the authors speculated resulted in the possible secondary death of the fetuses in utero. The authors reported that 70 percent of the control dams delivered on day 21 of pregnancy, while only 18 percent of the treated dams did ($p < 0.05$).

The Panel noted that Lewis and Schulman (Ref. 7) reported the results of a 20-year retrospective study designed to evaluate the influence of aspirin on the duration of human gestation and labor of 103 aspirin-treated subjects. The study compared subjects (most of whom had nonspecific collagen disease or degenerative musculoskeletal disease) taking doses of greater than 3,250 mg of aspirin a day during the last 6 months of pregnancy to two control groups. One of the control groups consisted of 52 pregnant females with rheumatoid arthritis, nonspecific collagen diseases, or degenerative musculoskeletal disease who did not take aspirin or other compounds known to affect prostaglandin synthesis. The second control group consisted of 50 pregnant women without known disease who did not take therapeutic doses of aspirin or related drugs. The authors reported that subjects taking aspirin had an average gestation period of over 1 week longer than either of the control groups ($p < 0.025$) and that the control groups did not differ from each other. In the aspirin group, 42 percent of the subjects had gestation periods of greater than 42 weeks (at least 15 days post mature), while only 3 percent of the combined control group demonstrated this. The authors considered this result as very significant ($p < 0.0001$). The subjects in the aspirin group also had a significant longer mean length of labor than either of the control groups (12 hours versus 7 hours, p-value of less than 0.005) and had an estimated average blood-loss at delivery of 100 mL more than either of the control groups ($p < 0.025$).

The Panel evaluated a study by Collins and Turner (Ref. 8) in which two groups of pregnant women who self-medicated with analgesics regularly were compared to a group of matched controls. One group of subjects (constant takers) admitted to taking analgesics every day of their pregnancy. Many of the women in this group had self-medicated with analgesics for years and were habituated to analgesics. The constant takers took analgesic powders containing either aspirin, salicylamide, and caffeine or aspirin, phenacetin, and caffeine. The second group of self-medicated women (intermittent takers) admitted to taking analgesics at least once a week throughout their pregnancy. However, the authors reported that many of the women in this group took analgesics much more frequently than this, but denied taking them every day. The women in this group took the same analgesic powders or a variety of tablets containing salicylate alone or in combination with other drugs. None of the subjects took aspirin for chronic disease such as rheumatoid arthritis.

Collins and Turner reported that the major effects of regular aspirin consumption on pregnancy were an increased frequency of anemia during pregnancy, a prolonger gestation, an increased incidence of complicated deliveries, a high incidence of antepartum and postpartum hemorrhage and transfusion at delivery, and an increased perinatal mortality. The authors theorized that the observed effects may have been caused by the other constituents of the powders or by the fact that so many of the regular takers were heavy smokers. The authors stated, however, that the observed effects of the study were also explainable by the pharmacologic effects of aspirin.

The mean length of pregnancy of the two groups of women was significantly increased compared to the control group ($p < 0.05$). The authors of the study reported that women in the control group had a mean duration of pregnancy of 38.7 weeks while the women in the aspirin groups had a mean duration of pregnancy of 39.7 and 39.8 weeks, respectively. The proportion of subjects going beyond 42 weeks of pregnancy was increased but not significantly so. The authors stated that the inhibition of prostaglandin release by aspirin might be expected to delay the onset of labor and increase the mean length of labor.

The authors reported a highly significant increase in both prenatal and postnatal bleeding ($p < 0.001$). However, because the numbers in the survey were small, the findings in the present and past pregnancies of the women in the study were combined when assessing the incidence of antepartum hemorrhage, postpartum hemorrhage, and transfusion at delivery. The authors remarked that it was not possible to determine in each patient the time between the last dose of aspirin and delivery.

In a subsequent study (Ref. 9), Turner and Collins evaluated the effects of regular salicylate ingestion during

pregnancy on the infants of 144 mothers. Infants born to mothers who took salicylates daily during their pregnancy were compared to infants whose mothers took salicylates at least once a week and to a control group matched for age, parity, gravity, ethnic group, and social class. The authors reported that the birth-weights of infants born to mothers taking salicylates were significantly lower than those of the matched controls even after a correction for the mothers who smoked during the study. The perinatal mortality of these infants was increased. The authors reported that while a direct comparison between salicylate levels in maternal blood and cord blood was not possible because of inconsistencies in the sampling of maternal blood, high levels of salicylates in maternal blood corresponded to high salicylate levels in cord blood. However, no clinical signs of bleeding in the infants with increased salicylate blood levels were reported.

Bleyer and Breckenridge (Ref. 10) studied the effects of prenatal medications, including aspirin, on newborn hemostasis by the comparison of prenatal histories obtained from prenatal medication diaries with clinical and laboratory studies done postpartum. Forty-Three newborns, all born of healthy mothers after normal pregnancies and uneventful deliveries, were included in the study. A medication diary designed to provide an accurate record of all pharmacological agents taken during pregnancy was kept by each mother in the study and brought to the hospital at the time of delivery. Only after all clinical and laboratory data had been tabulated were the medication records opened and the mothers who had taken aspirin identified and allocated to the following groups. The drug group consisted of infants whose mother took more than 0.3 g of aspirin during the week prior to delivery. The dosage range for this group ranged from 0.32 g taken once 7 days before delivery to 1.3 g daily. The control group consisted of infants whose mothers had not taken aspirin in any form during the last 3 weeks of their pregnancy. Fourteen infants exposed to aspirin during the week prior to birth were compared to 17 infants in the control group. The authors of the study stated that they had chosen the above criteria based on information that had established that blood levels can be detected for 2 days or longer in adults and for as long as 7 days in neonates, and that a single small dose of aspirin (0.15 to 1.5 g) in normal adults can cause hemostatic abnormalities for as long as 7 days.

Umbilical cord and maternal blood samples were obtained at the time of delivery. All bleeding, including hemorrhage from circumcision, was recorded. Guaiac and fetal hemoglobin tests were performed on meconium from each newborn. A variety of laboratory tests relating to platelet function and number and clotting factor activities were performed on both the maternal and neonatal blood. The authors reported that maternal ingestion of aspirin was associated with the inhibition of collagen-induced platelet aggregation and diminished factor XII activity and noted that both were evidenced after ordinary doses of aspirin occurring in the newborn when the mother ingested as little as 0.65 g of aspirin as long as 2 weeks prior to delivery.

The authors stated that the diminished factor XII activity is of uncertain clinical importance but that aspirin-induced platelet dysfunction may have clinical relevance, particularly during difficult, traumatic deliveries or in the presence of another hemostatic defect such as von Willebrand's disease, hemophilia, or thrombocytopenia. They concluded that even though none of the newborns included in the study developed major hemorrhages, the hemostatic defects uncovered by the study are not necessarily benign, and recommended that until the clinical significance of the study finding is further evaluated, aspirin and other anti-inflammatory agents known to produce platelet dysfunction should be avoided when labor is imminent.

The Panel also noted a report (Ref. 11) by Haslam, Ekert, and Gillam of a case of a "life-threatening gastrointestinal hemorrhage" requiring two transfusions in one infant whose mother had taken calcium carbaspirin (3 tablets of 300 mg on each of the last 3 days of pregnancy, a total of 2,700 mg).

The more recent data address some of the Panel's concerns. As noted above, the studies by Brent, Shook, and Wilson on the effects of aspirin exposure in the third trimester and the last month of pregnancy (Refs. 3 and 4) included an evaluation of stillbirths, length of gestation, and length of labor. The authors reported that the data indicated that there was no statistically significant association between aspirin and still birth for aspirin exposure during the third trimester of pregnancy.

The unadjusted 3-month exposure data on the length of gestation from this study suggest that the average gestation period of 39.8 weeks for the unexposed group was significantly increased by 0.1 week for any exposed aspirin group ($p=0.004$) and decreased 0.2 week for the high dose aspirin group ($p=0.012$). However, the authors reported that the adjustment of the data for covariables by multiple regression indicated that the effect of aspirin alone does not significantly change the length of gestation in any of the three groups analyzed. The unadjusted data from the low and high dose aspirin use during the last month of pregnancy suggest a significant decrease in the length of gestation of 0.1 week for the high dose group ($p=0.022$) which is supported by the multiple regression analysis of the data. When the data were adjusted, statistically significant decreases were indicated for both groups (low dose mean decrease of 0.097 week, $p=0.014$; high dose mean decrease of 0.191 week, $p=0.0001$). The authors reported that the data were sufficient to detect a difference of 0.84 day (0.12 week) for the 3-month data and 0.7 day (0.1 week) for the 1-month data between the exposed populations and the unexposed populations, with a power of 90 percent or greater.

With regard to the length of labor, the authors reported that based on the unadjusted data none of the third-trimester aspirin exposure levels resulted in a statistically significant change in the mean delivery time of 7.7 hours for the unexposed group. However, they did report that the high dose data suggest an average decrease of 0.4 hour in length of labor, which was not significant. When the above data were adjusted for covariables, there was a small but statistically significant increase in the length of labor for the any-aspirin group (mean increase=0.467 hour, $p=0.042$) and for the high-dose group (mean increase=0.644 hour, $p=0.040$). In the last-month exposure data, no significant increase in the length of labor was found for the high-dose group, but the data for the low-dose group indicated an increase of 0.5 hour (unadjusted data) and 0.315 hour (adjusted) ($p=0.016$). The authors report that the data were sufficient to detect a difference of 18 minutes (0.3 hour) between any-aspirin users and nonusers, with a power of 90 percent or greater.

In the portion of the study in which the authors attempted to assess if there was a dose effect among differing aspirin groups, the authors compared the data (adjusted for covariables) on gestation from subjects with any exposure to aspirin to unexposed women and reported that aspirin alone did not increase the average gestation period. The authors further reported that when the 3-month high- and low-dose

groups were considered, the high-dose group had a slightly decreased gestation period (0.2 week). However, when these data were adjusted for covariables, the data did not indicate an aspirin effect on the length of gestation. The authors reported similar results when evaluating the subjects with exposure only in the last month.

No effect of aspirin on the length of labor was reported in the study when the unadjusted data from the any-exposure-to-aspirin group were compared to unexposed subjects. However, the adjustment of the data for covariables indicated that aspirin alone would be associated with a slight increase in the length of labor of about 28 minutes for the exposed groups. When dose during the last trimester was considered for this outcome, the high-dose aspirin group had an average labor of 24 minutes less than the unexposed group. When the data were adjusted for covariables, aspirin exposure along was indicated to be associated with an average increase of about 39 minutes. No difference was indicated for the low-dose group. Data from the last-month exposure groups indicated no increase for the high dose group but a slight increase for the low-dose group. Adjustment for covariables indicated that aspirin exposure alone was associated with an average increase of 21 minutes in the low-dose group, but there was no increase in the high-dose group.

In addition, the agency is aware of new uses of aspirin that have been reported in the scientific literature (Refs. 1 and 2). Schiff et al (Ref. 1) reported a prospective, randomized, double-blind, placebo-controlled study to investigate the capacity of aspirin to prevent pregnancy-induced hypertension and to alter prostaglandin metabolism in women at risk from these disorders. The results of the study indicated that the number of women in whom pregnancy-induced hypertension developed was significantly lower among women treated with 100 mg of aspirin daily during the last trimester of pregnancy (to within 0 days of delivery) than in the placebo group. The same result was reported for the incidence of preeclamptic toxemia. Based on this study, the authors concluded that low daily doses of aspirin taken during the third trimester significantly reduce the incidence of pregnancy-induced hypertension and preeclamptic toxemia of pregnancy in women at risk from these disorders.

Benigni et al. (Ref. 2) evaluated the effect of low-dose aspirin on the fetal generation of thromboxane by platelets in women at risk for pregnancy-induced hypertension. The authors reported that low doses (60 mg daily until delivery) of aspirin suppressed maternal platelet thromboxane B_2, but only partially suppressed neonatal platelet thromboxane B_2, thus allowing hemostatic competence of the fetus and newborn. The authors also reported that low doses of aspirin were associated with a longer pregnancy and an increased weight of newborns.

The agency concludes that the effects of these ingredients on maternal and fetal vascular and platelet prostaglandins have been demonstrated. These effects could be beneficial in some instances, e.g., pregnancy-induced hypertension, or under other circumstances could cause problems in some mothers and infants. These effects could lead to complications for some women during delivery, and these problems would be most likely to occur if aspirin were taken during the last trimester of pregnancy close to the time that delivery occurs. Although the agency has not yet evaluated these potential new uses of aspirin, the agency is concerned that a reference to bleeding as included in the proposed warning may discourage compliance with medically supervised uses of aspirin, e.g., the treatment of chronic arthritis, and therefore is not including a specific reference to bleeding in the new warning for these OTC drug products.

The agency notes that another OTC analgesic drug, ibuprofen, which is not currently included in the OTC drug review but is the subject of an approved new drug application, bears a similar warning, which states:

IT IS ESPECIALLY IMPORTANT NOT TO USE IBUPROFEN DURING THE LAST 3 MONTHS OF PREGNANCY UNLESS SPECIFICALLY DIRECTED TO DO SO BY A DOCTOR BECAUSE IT MAY CAUSE PROBLEMS IN THE UNBORN CHILD OR COMPLICATIONS DURING DELIVERY.

Both aspirin and ibuprofen are members of a class of drug ingredients known as non-steroidal anti-inflammatory drugs. The basis for the pharmacologic action of this drug class is their ability to inhibit the synthesis of prostaglandins (Ref. 12). The inhibition of prostaglandin synthesis is a critical factor with regard to the effects of aspirin on pregnancy. Aspirin and the other members of this class share similar effects on prostaglandin synthesis, and their effects on pregnancy are similar (Refs. 13 and 14). The agency now believes that having different warnings on OTC drug products containing these ingredients could cause consumers to perceive that there is a difference in the safety of using these ingredients during the third trimester of pregnancy when, in fact, there is no established significant safety difference.

For all of the above reasons, the agency has concluded that it would be advisable to include in the labeling of all OTC aspirin and aspirin-containing drug products a warning statement that it is especially important not to use these products during the last 3 months of pregnancy unless specifically directed to do so by a doctor and to inform pregnant women why they should not do so, i.e., because such use of the drug may cause problems in the unborn child or cause complications during delivery. Therefore, the agency is amending the pregnancy-nursing warning labeling requirement in § 201.63 to require that all oral and rectal OTC aspirin and aspirin-containing drug products bear a warning similar to that currently required for OTC ibuprofen drug products, as follows:

IT IS ESPECIALLY IMPORTANT NOT TO USE (select "ASPIRIN" or "CARBASPIRIN CALCIUM," as appropriate) "DURING THE LAST 3 MONTHS OF PREGNANCY UNLESS SPECIFICALLY DIRECTED TO DO SO BY A DOCTOR BECAUSE IT MAY CAUSE PROBLEMS IN THE UNBORN CHILD OR COMPLICATIONS DURING DELIVERY.

The agency is requiring that this warning immediately follow the general pregnancy warning required by § 201.63(a) and appear in boldface type and all capital letters.

The agency disagrees with the comments that contended that the proposed third-trimester warning is unnecessary when used in conjuction with the general pregnancy-nursing warning, that the two warnings used together would reduce the likelihood that consumers will follow the directions of the general warning, that the third-trimester warning would result in the inappropriate use of the OTC aspirin drug products during pregnancy, and that the two warnings used together may confuse and unduly frighten consumers. The general pregnancy-nursing warning regulation (§ 201.63(b)) provides that where a specific warning relating to use during pregnancy has been established for a particular drug, the specific warning shall be used in place of the general warning unless otherwise stated. In this particular situation, the agency concludes that each warning statement serves a specific purpose. The general pregnancy-nursing warning is intended to convey the message that at any time during pregnancy a consumer should seek the advise of a health professional

before using any OTC drug product. The third-trimester warning is intended to emphasize that it is especially important not to use these types of drugs during this time unless specifically directed to do so by a doctor. The agency has revised the proposed warning in this final rule to reflect that intent. Thus, the agency does not intend, in this case, for the third-trimester warning to be used in place of the general warning. The third-trimester warning is to be used in addition to the general warning. The final regulation specifically states this requirement.

The similar warning for OTC ibuprofen drug products has been in use for over 5 years. It too is used in conjuction with the general pregnancy-nursing warning. The agency has not received any reports that the use of both of these warnings has been confusing or frightening to consumers.

The agency is not adopting the warning recommended by the trade association which reads "Do not use this product during the last 3 months of pregnancy unless advised to do so by a doctor because it may cause problems during delivery." The agency concludes that the ibuprofen-type warning that has been adopted is more informative to consumers because it provides more information about the potential risks that may occur.

The agency believes that it is important that this new labeling information be brought to consumers' attention. In order to ensure that the new thrid-trimester pregnancy warning for OTC aspirin and aspirin-containing drug products is prominently displayed, the agency is requiring that the warning be printed on all labeling in boldface type and all capital letters. Based on the format of the new warning, the agency does not consider it appropriate to combine any portion of the warning with the general pregnancy-nursing warning statement. Further, the agency does not want the general pregnancy-nursing warning to appear in different wording in the labeling of OTC aspirin and aspirin-containing drug products. Therefore, the agency is not including in this final rule a provision that the two pregnancy-warning statements can be combined to eliminate duplicative words and phrases.

Further, the agency is not adopting the combined warning suggested by the comment that requested a hearing, which read, "As with any drug, if you are pregnant or nursing a baby, do not take unless directed by a doctor. This is particularly important for aspirin during the last three months of pregnancy since it may cause bleeding problems in mother or child." This combined warning would change the general pregnancy-nursing warning required by § 201.63. As noted above, the agency does not want this warning when used in the labeling for aspirin-containing products to be different than the warning that appears on all other OTC drug products intended for systemic absorption. In addition, "bleeding problems" are no longer included specifically in the warning; thus, the comment's suggested warning would not be appropriate to use. For these reasons, the agency concludes that the comment's request for a hearing is moots.

The effective date of this final rule is August 6, 1990. Although the regulation will become effective on that date, manufacturers of affected drug products will be permitted to defer labeling changes until July 5, 1991. Thereafter, covered OTC drugs initially introduced or initially delivered for introduction into interstate commerce will be required to comply with the new labeling requirement. The agency will consider requests for additional time to comply with the requirement based on a showing of good cause. Such requests should be sent to Office of Compliance, Center for Drug Evaluation and Research, HFD–300, Food and Drug Administration, 5600 Fishers Lane, Rockville, Maryland 20857. Any request for additional time must state the reasons that the drug product's compliance with the labeling requirement cannot be achieved, steps that have been taken to achieved compliance, and when compliance is anticipated. Requests for additional time must be specifically granted by the agency; an extension of time will not be considered granted merely upon submission of a request. Manufactures are therefore encouraged to submit requests for extensions of time far enough in advance to allow the agency time to act on them.

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(5) Comments No. C182, Docket No. 77N–0094, Dockets Management Branch.

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V. Economic Impact

FDA has examined the regulatory impact and regulatory flexibility implications of the final rule in accordance with Executive Order 12291 and the Regulatory Flexibility Act (Pub. L. 96–354). This final regulation imposes direct one-time costs associated with changing product labels to include the third-trimester pregnancy warning statement. FDA estimates those costs to total less than $5 million. Therefore, the agency has determined that the final rule is not a major rule as defined in Executive Order 12291. Further, the agency certifies that this final rule will not have a significant economic impact

on a substantial number of small entities as defined by the Regulatory Flexibility Act.

VI. Environmental Impact

The agency has determined under 21 CFR 25.24(c)(6) that 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.

List of Subjects in 21 CFR Part 201

Drugs, Labeling, Reporting and recordkeeping requirements.

Therefore, under the Federal Food, Drug, and Cosmetic Act, subchapter D of chapter I of title 21 of the Code of Federal Regulations is amended in part 201 as follows:

PART 201—LABELING

1. The authority citation for 21 CFR part 201 continues to read as follows:

Authority: Sections 201, 301, 501, 502, 503, 505, 506, 507, 508, 510, 512, 701, 704, 706 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 321, 331, 351, 352, 353, 355, 356, 357, 358, 360, 360b, 371, 374, 376); secs. 215, 301, 351, 354–360F, 361 of the Public Health Service Act (42 U.S.C. 216, 241, 262, 263b–263n, 264).

2. Section 201.63 is amended by adding new paragraph (e) to read as follows:

§ 201.63 Pregnancy-nursing warning.

* * * * *

(e) The labeling of orally or rectally administered OTC aspirin and aspirin-containing drug products must bear a warning that immediately follows the general warning identified in paragraph (a) of this section. The warning shall be as follows:

"IT IS ESPECIALLY IMPORTANT NOT TO USE" (select **"ASPIRIN"** or **"CARBASPIRIN CALCIUM,"** as appropriate) **"DURING THE LAST 3 MONTHS OF PREGNANCY UNLESS SPECIFICALLY DIRECTED TO DO SO BY A DOCTOR BECAUSE IT MAY CAUSE PROBLEMS IN THE UNBORN CHILD OR COMPLICATIONS DURING DELIVERY."** [sentence in bold face type and all capital letters]

Dated: May 23, 1990.

James S. Benson,

Acting Commissioner of Food and Drugs.

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BILLING CODE 4160–01–M