

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Parts 201, 310, 341, and 369

[Docket No. 76N-052H]

Cold, Cough, Allergy, Bronchodilator, and Antiasthmatic Drug Products for Over-the-Counter Human Use; Tentative Final Monograph for OTC Antihistamine Drug Products

AGENCY: Food and Drug Administration.

ACTION: Notice of proposed rulemaking.

SUMMARY: The Food and Drug Administration (FDA) is issuing a notice of proposed rulemaking that amends the tentative final monograph (proposed rule) for over-the-counter (OTC) antihistamine drug products (drug products used for the relief of the symptoms of hay fever and upper respiratory allergies (allergic rhinitis) and the symptoms of sneezing and runny nose associated with the common cold) to include chlorcyclizine hydrochloride and doxylamine succinate and to revise the proposed dosage for triprolidine hydrochloride. FDA is issuing this notice of proposed rulemaking after considering the report and recommendations of the Advisory Review Panel on OTC Cold, Cough, Allergy, Bronchodilator, and Antiasthmatic Drug Products, public comments on an advance notice of proposed rulemaking that was based on those recommendations, and several comments submitted in response to the previous tentative final monograph for OTC antihistamine drug products that was published in the *Federal Register* of January 15, 1985 (50 FR 2200). This proposal is part of the ongoing review of OTC drug products conducted by FDA.

DATES: Written comments, objections, or requests for oral hearing on the proposed regulation before the Commissioner of Food and Drugs by October 23, 1987. New data by August 24, 1988. Comments on the new data by October 25, 1988. Written comments on the agency's economic impact determination by December 22, 1987.

ADDRESS: Written comments, objections, new data, or requests for oral hearing to the Dockets Management Branch (HFA-305), Food and Drug Administration, Rm. 4-62, 5600 Fishers Lane, Rockville, MD 20857.

FOR FURTHER INFORMATION CONTACT: William E. Gilbertson, Center for Drugs and Biologics (HFN-210), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301-295-8000.

SUPPLEMENTARY INFORMATION: In the *Federal Register* of September 9, 1976 (41 FR 3812), 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 cold, cough, allergy, bronchodilator, and antiasthmatic drug products, together with the recommendations of the Advisory Review Panel on OTC Cold, Cough, Allergy, Bronchodilator, and Antiasthmatic Drug Products (Cough-Cold Panel), which was the advisory review panel responsible for evaluating data on the active ingredients in these drug classes. Interested persons were invited to submit comments by December 8, 1976. Reply comments in response to comments filed in the initial comment period could be submitted by January 7, 1977.

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 (address above), after deletion of a small amount of trade secret information. Data and information received after the administrative record was reopened have also been put on display in the Dockets Management Branch.

In the advance notice of proposed rulemaking, the Cough-Cold Panel recommended that doxylamine succinate be generally recognized as safe and effective as an OTC antihistamine (41 FR 38419). After the Panel's report was published, controversy arose concerning whether or not there is an association of a prescription drug product containing doxylamine succinate with birth defects. This drug product was prescribed as an antinauseant for use during pregnancy. The scientific and medical communities were actively discussing and debating whether doxylamine succinate, in fact, plays a causal role in reported birth defects.

In the *Federal Register* of January 15, 1985 (50 FR 2200), FDA published a tentative final monograph (proposed rule) on OTC antihistamine drug products. Because of the unresolved issues concerning doxylamine succinate and birth defects, when this tentative final monograph was published in the *Federal Register*, the agency reserved detailed discussion and acknowledged the need to evaluate new data and information concerning the relationship between doxylamine succinate and birth defects (50 FR 2202). After reviewing and evaluating extensive data concerning the safety of doxylamine succinate, the agency is proposing in

this document that this ingredient be Category I. (See comment 1 below.)

The agency is also proposing in this amendment that chlorcyclizine hydrochloride, an ingredient that was not reviewed by the Cough-Cold Panel, be generally recognized as safe and effective as an OTC antihistamine drug product. (See Part II. below—the Agency's proposals concerning Chlorcyclizine Hydrochloride.) In addition, the agency is revising the dosage for the ingredient triprolidine hydrochloride. (See comment 7 below.)

In response to the advance notice of proposed rulemaking, nine professionals, two manufacturers, two professional societies, and one individual submitted comments concerning doxylamine succinate. These comments are addressed in this document. In response to the tentative final monograph, one law firm and two manufacturers submitted comments that are also addressed in this document. Copies of the comments received are on public display in the Dockets Management Branch.

This proposed rule amends the previous tentative final monograph on antihistamine drug products that was published in the *Federal Register* of January 15, 1985 (50 FR 2200) in Subpart B, by adding the ingredients chlorcyclizine hydrochloride and doxylamine succinate in § 341.12; and in Subpart C, by adding warnings and directions for chlorcyclizine hydrochloride and doxylamine succinate and revised directions for triprolidine hydrochloride in §§ 341.72 and 341.90. In addition, parts of §§ 341.12, 341.72, and 341.90 have been redesignated to reflect the addition of these two additional antihistamine ingredients. This amendment constitutes FDA's tentative adoption of the Panel's conclusions and recommendations on OTC antihistamine drug products, as modified on the basis of the comments received and the agency's independent evaluation of the Panel's report. Modifications have been made for clarity and regulatory accuracy and to reflect new information. Such new information has been placed on file in the Dockets Management Branch (address above). These modifications are reflected in the following summary of the comments and FDA's responses to them.

All "OTC Volumes" cited throughout this document refer to the submissions made by interested persons pursuant to the call-for-data notice published in the *Federal Register* of August 9, 1972 (37 FR 16029) or to additional information that has come to the agency's attention since

publication of the advance notice of proposed rulemaking. The volumes are on public display in the Dockets Management Branch.

I. The Agency's Tentative Conclusions on the Comments

A. Comments on Doxylamine Succinate

1. One comment, submitted in response to the tentative final monograph, provided data to support the Category I status of doxylamine succinate as an OTC antihistamine active ingredient. The comment contended that the results of available animal and human studies amply support the position that doxylamine succinate is safe for use during pregnancy. The comment discussed the results of two studies by Eskenazi and Bracken (Ref. 1) and Aselton et al. (Ref. 2), cited in the antihistamine tentative final monograph (50 FR 2201 to 2202). These studies found an association between a prescription drug product containing doxylamine succinate and the occurrence of pyloric stenosis in infants. The comment cited the following flaws in the Eskenazi and Bracken study (Ref. 1): (1) the "very small" numbers of subjects in the study, i.e., 1,747 pregnancies in which six cases of pyloric stenosis occurred in drug-exposed infants; (2) the lack of evaluation of other causative factors for pyloric stenosis such as a family history (particularly for the mother) of the occurrence of pyloric stenosis, psychological stress during pregnancy, low levels of the hormone gastrin in the mother, and the nausea and vomiting of pregnancy per se; (3) the patient selection for the study; and (4) the method of categorizing congenital defects in the study. The comment also stated that, although the findings of the second study by Aselton et al. (Ref. 2) were consistent with the Eskenazi and Bracken study (Ref. 1), the number of cases studied in the second study were also "very small." The comment also noted that the authors of the second study stated that the disorder could result from the underlying nausea and vomiting of pregnancy or some other cause.

The comment noted that the authors of both of these "small" studies (Refs. 1 and 2) warned against any interpretations of a causal relationship between maternal drug exposure and the occurrence of pyloric stenosis based upon their data. Aselton et al. (Ref. 2) stated in their study that "in view of the conflicting results and the absence of any apparent biologic basis for a connection between [the prescription drug containing doxylamine succinate]

and pyloric stenosis, explanations for the current findings other than a causal relation must be considered and given substantial weight." Other explanations cited by the comment for the findings in the Eskenazi and Bracken and the Aselton et al. studies (Refs. 1 and 2) include Eskenazi and Bracken's recognition that pyloric stenosis may in fact result from a genetic predisposition, in which case a manifestation of the disease would then be precipitated by environmental factors. Also, mothers who themselves had had pyloric stenosis or were predisposed toward it may have been more nauseated and therefore more likely to have taken the prescription drug containing doxylamine succinate during pregnancy. The comment noted that this explanation of the cause of pyloric stenosis has also been recognized in a study (Ref. 3) whose authors include some of the authors in the Aselton et al. study (Ref. 2).

The comment discussed another much larger case-control study by Mitchell et al. (Ref. 4), also cited by the agency in the tentative final monograph, that compared the incidence of pyloric stenosis in infants exposed to the prescription drug containing doxylamine succinate with infants who were not exposed to the drug. According to the comment, the findings in this study, involving 325 infants with pyloric stenosis, showed there was no increase in the occurrence of pyloric stenosis among infants whose mothers took the prescription drug containing doxylamine succinate.

The comment also discussed a prospective study by Rosa et al. (Ref. 5), cited by the agency in the tentative final monograph that used Medicaid data from Michigan. According to the comment, this study also did not support an association between maternal exposure to the prescription drug containing doxylamine succinate and the occurrence of pyloric stenosis in infants. The comment noted that this study, like that of Mitchell et al. (Ref. 4), has a much higher statistical power than the Eskenazi and Bracken study (Ref. 1) and the Aselton et al. study (Ref. 2).

In addition, the comment cited a letter to the editor of the *American Journal of Obstetrics and Gynecology* (Ref. 6) that reviewed the experience of the Royal College of General Practitioners in England and concluded that pyloric stenosis is associated with nausea and vomiting in pregnancy rather than with any specific drug. The comment cited a personal communication from Michaelis (Ref. 7) containing a review of the extensive data of the German Research

Society and concluding that there was no association between maternal exposure to the prescription drug containing doxylamine succinate and the occurrence of pyloric stenosis in infants. According to the comment, another study by Milkovich and Van Den Berg (Ref. 8) did not support an association between maternal exposure to the prescription drug and the occurrence of pyloric stenosis.

The comment also discussed expert testimony in a trial that focused on the sole question of whether the prescription antinauseant containing doxylamine succinate causes birth defects. The comment stated that this culminated on March 12, 1985 with a verdict firmly answering that question in the negative (*In re: Richardson-Merrell "Bendectin" Products Liability Litigation*, MDL No. 486 (S.D. Ohio 1985)). The comment explained that, in this trial, the alleged association between the prescription drug containing doxylamine succinate and pyloric stenosis was addressed by expert witnesses. One expert, who had published several papers concerning pyloric stenosis in scientific journals, testified that pyloric stenosis is not actually a birth defect but is triggered by something in the environment after birth and has nothing to do with doxylamine succinate. He also testified that the evidence from both case control and cohort studies on the prescription antinauseant containing doxylamine succinate indicates that the drug does not cause birth defects in children exposed to the drug in utero. Another expert was coauthor of the hypothesis generating study concerning exposure to the prescription drug containing doxylamine succinate and pyloric stenosis (Ref. 1). He testified that, based upon the epidemiologic data from his own study (Ref. 1), the Aselton et al. study (Ref. 2), and the Mitchell et al. study (Ref. 4), no association between the drug and pyloric stenosis has been established. He added that it cannot possibly be said that this drug has any causal relationship to pyloric stenosis, which results from a genetic predisposition to this condition. The comment concluded "that pyloric stenosis in newborns is not due to exposure to [the prescription drug product containing doxylamine succinate], but to the mother's predisposition toward both pyloric stenosis and nausea which caused the mothers to be prescribed [the drug product containing doxylamine succinate]."

The comment cited a large double-blind primate study, designed

specifically to examine a possible association between maternal exposure to the prescription drug containing doxylamine succinate and ventricular septal defects (Ref. 9). According to the comment, this study found no evidence in monkeys of an association between exposure to the prescription drug and birth defects of any kind, including the occurrence of pyloric stenosis.

The comment cited major reviews in the literature concerning possible teratogenicity of the prescription drug containing doxylamine succinate (Refs. 11 and 12). The comment stated that neither of these reviews found evidence of such a relationship. The comment submitted citations for several editorials in scientific journals that support the safety of the prescription drug (Refs. 13, 14, and 15). The comment also included additional citations for the published human experience with the drug (Refs. 16 through 39).

The comment concluded that the existing data support the safety of doxylamine succinate for OTC use and stated that an additional warning regarding the use of drug products containing doxylamine succinate during pregnancy is unwarranted. Therefore, according to the comment, the ingredient doxylamine succinate should not be eliminated from the tentative final monograph for OTC antihistamine drug products.

The agency has reviewed the extensive body of data available concerning the safety of doxylamine succinate and concludes that this ingredient is safe for use as an OTC antihistamine drug product. Based on the data, the agency is proposing a Category I classification for doxylamine succinate in this tentative final monograph.

Pyloric Stenosis

A major concern was identified in the previous tentative final monograph (50 FR 2200) regarding the safety of doxylamine succinate in OTC antihistamine drug products used during pregnancy. The concern related to a possible link between the use of antinauseant drugs containing doxylamine succinate and the occurrence of pyloric stenosis in infants. As noted above, Eskenazi and Bracken (Ref. 1) observed a significant association (odds ratio=1.40) between the occurrence of pyloric stenosis in infants and in utero exposure to an antinauseant drug containing doxylamine succinate. The investigators did not find other significantly increased risks for congenital malformations, except for a possible association of exposure to this drug in utero with heart

valve anomalies (odds ratio=2.99). The case subjects were mothers of congenitally malformed infants, newborn or stillborn, at five urban hospitals in central Connecticut between May 1974, and November 1976, and mothers of malformed infants who were referred to one of the five hospitals before the child was 1 year of age. Control subjects were mothers of healthy newborn infants born in the five hospitals between November 1974, and November 1976. Case and control mothers were interviewed in the hospital or at home by trained interviewers using a standardized questionnaire. Data collected included demographic variables, smoking history, pregnancy history, drug use, and exposure to other possible risk factors. Data were analyzed from 1,369 cases and 2,968 controls. In 6.3 percent of the cases, mothers of malformed infants reported using the antinauseant drug containing doxylamine succinate. Also, 4.6 percent of control mothers (normal infants) reported using the drug. Therefore, mothers of malformed infants had a 40-percent overall increased chance of being exposed to the antinauseant drug in the first trimester of pregnancy (odds ratio=1.40 with 95 percent confidence limits of 0.96 and 2.05, $p=0.08$). The investigators found some evidence that there was a synergistic relationship between smoking and use of the antinauseant drug to case-control status, i.e., women who used the antinauseant drug and were smokers had increased odds ratios for the occurrence of birth defects of 2.36 (light smokers) and 6.39 (heavy smokers). However, the synergistic relationships were statistically significant only for the combined group of smokers, i.e., both light and heavy smokers (odds ratio=2.91 with 95 percent confidence limits of 1.14 and 7.46). The investigators also found that infants with pyloric stenosis were more than four times likely to have mothers who reported using the antinauseant drug (odds ratio=4.33 with 95 percent confidence of 1.75 and 10.75, $p<0.001$). Antinauseant drug use was also associated with a threefold increased risk for defective heart valves in the offspring (odds ratio=2.99 with 95 percent confidence limits of 1.02 and 8.74, $p<0.04$). No other associations between antinauseant drug use during the first trimester of pregnancy and the occurrence of specific birth defects were statistically significant. When additional statistical procedures were applied to the data to account for the number of associations evaluated in the study (16), it was found that $p=0.003$ was equivalent to the usual $p<0.05$ level for

statistical significance. By this criterion, only the association between antinauseant drug use and pyloric stenosis was significantly larger than might be expected. Analysis for possible confounding variables for the association between antinauseant drug use and pyloric stenosis did not yield any statistically significant differences between case and control mothers. The investigators discussed other findings in the literature concerning associations between the use of the antinauseant drug containing doxylamine succinate and the occurrence of gastrointestinal malformations. The investigators stated that "because gastrointestinal atresias, like pyloric stenosis, are constrictions of the digestive tract, it is plausible that a similar mechanism, such as the faulty innervation of the abdominal visera either by the vagus or the parasympathetic ganglia, may be involved in the etiology of these malformations." The investigators concluded that "more than 1 in 10 cases of pyloric stenosis may be due to maternal use of [the antinauseant drug containing doxylamine succinate]." As the comment above pointed out, the investigators in this study also discussed possible confounding factors for the association between antinauseant drug use and the occurrence of pyloric stenosis. These factors included a genetic predisposition to pyloric stenosis that could be precipitated by environmental factors, the possibility that mothers who themselves had pyloric stenosis or were predisposed to it may be more likely to be nauseated during pregnancy and therefore more likely to use antinauseant drugs during pregnancy, and a strong sex differential observed among pyloric stenosis cases with 7.8 male cases per every female case. The investigators also stated that whether the association between use of the antinauseant drug and the occurrence of pyloric stenosis is a direct causal relationship is unclear.

In another study discussed by the comment above, Aselton et al. (Ref. 2) studied long-term follow up of structural disorders present at birth or shortly thereafter in infants born at the Group Health Cooperative of Puget Sound. Out of 13,346 births, the investigators identified all infants with a diagnosis of pyloric stenosis, confirmed by surgery, born between July 1, 1977, and June 30, 1982. Automated pharmacy profiles were examined for maternal use in the first trimester of pregnancy of an antinauseant drug containing doxylamine succinate. This examination was to determine if an association

existed between maternal use of the drug and the occurrence of pyloric stenosis in infants. Among the 3,835 mothers obtaining prescriptions for the antinauseant drug containing doxylamine succinate, 13 (3.4/1,000) delivered infants who developed pyloric stenosis. Among the 9,511 mothers who did not obtain the drug, 13 (1.4/1,000) delivered infants who developed pyloric stenosis. The resulting risk-ratio estimate for drug-exposed infants compared to nonexposed infants was 2.5 with a 95 percent confidence interval of 1.2 to 5.2. When the mothers were divided according to the number of prescriptions filled during pregnancy, risk ratio estimates increased with increased numbers of prescriptions filled. A case-control approach was used to analyze the data. Twenty-five infants out of a cohort of 26 infants with pyloric stenosis and no other serious defect were matched with 4 control infants per case. Factors matched included maternal age, race, season and year of birth, and the sex of the infant. The investigators found no difference in maternal age for users and nonusers of the prescription drug containing doxylamine succinate, that the incidence of pyloric stenosis was six times greater for male infants than for female infants, that there was no material association between drug use and the sex or race of the infant, and that the risk ratio estimate was 2.3 for drug-exposed infants when they controlled for calendar time of birth by stratifying the data into 2-year periods. The investigators concluded that maternal age and calendar time of birth were not important confounding factors in the cohort analysis. Matched analysis for case-control comparisons yielded a risk ratio estimate of 2.3 for infants born to mothers who had obtained the prescription drug. Stratification for birth weight, length of gestation, and birth order had little effect on this risk ratio estimate. The odds ratios for drug ingestion during the 8th, 9th, and 10th weeks of gestation were higher than for other weeks of gestation. However, the investigators stated that "these results should be interpreted with caution due to the imprecision in estimating gestational ages in the study and the fact that data for individual weeks are not independent of one another." The investigators concluded that the study provides additional evidence supporting a connection between the use of the prescription drug containing doxylamine succinate and the occurrence of pyloric stenosis in infants or between the occurrence of severe nausea during pregnancy and the occurrence of pyloric

stenosis in infants. The authors state that "in the absence of a biologic explanation for this finding and in view of conflicting results from other studies, a causal interpretation for this association [between drug use and the occurrence of pyloric stenosis] is not yet warranted."

In a large case-control study, Mitchell et al. (Ref. 4) evaluated the hypothesis suggested by another study (Ref. 1) that maternal use during pregnancy of an antinauseant drug containing doxylamine succinate increases the risk of the occurrence of pyloric stenosis in infants. The investigators did not find evidence to support this hypothesis. The data were obtained through an ongoing surveillance program designed to detect previously unsuspected human teratogens and to evaluate existing hypotheses concerning the risks and safety of antenatal exposures to drugs. Three hundred twenty-five infants with pyloric stenosis, 3,153 control infants with other conditions, and a subset of 724 control infants, with defects that may have originated at any time in the pregnancy, were identified through a review of information obtained from hospital lists, surgical logs, and clinic or office records of hospitals, clinics, and physicians in participating centers in the surveillance program. Within 6 months of the birth of their child, mothers were interviewed by trained pediatric nurse interviewers, who used a structured questionnaire that elicits information on parental age, occupation, income, maternal medical history, and previous pregnancies. This study evaluated infants of mothers who were interviewed between March 1976 and October 1982. For analysis, the data were stratified by maternal decade of age and geographic region and were controlled for a large number of potentially confounding factors such as variables concerning family history of malformations, maternal characteristics, obstetric history, maternal disease, complications of pregnancy, exposures during pregnancy, infant characteristics, and maternal use during pregnancy of a three-component antinauseant drug (diethylamine hydrochloride, doxylamine succinate, and pyridoxine hydrochloride) or a two-component antinauseant drug (doxylamine succinate and pyridoxine hydrochloride). Among the 325 infants with pyloric stenosis, 56 (17 percent) were exposed in utero to one of the antinauseant drugs containing doxylamine succinate, while among the 3,153 infants with other malformations, 616 (20 percent) were exposed. Analysis of these data yielded a relative risk

estimate of 0.9 with a 95 percent confidence interval of 0.6 to 1.2 for the occurrence of pyloric stenosis in infants exposed to one of the antinauseant drugs. The corresponding data analysis for the 325 infants with pyloric stenosis and the 724 infants with defects that may have had their origins at any time in pregnancy yielded a relative risk estimate of 1.0 with a 95 percent confidence interval of 0.7 to 1.4. Because inguinal hernia, like pyloric stenosis, may develop late in pregnancy or soon after birth, the investigators compared the in utero rate of exposure to one of the antinauseant drugs containing doxylamine succinate for the 325 infants with pyloric stenosis and for 608 control infants with inguinal hernia. They found a relative risk estimate of 0.8 with a 95 percent confidence interval of 0.6 to 1.2. The investigators concluded that "the present findings suggest that exposure to [an antinauseant drug containing doxylamine succinate] during pregnancy, whether early or late, does not increase the risk of pyloric stenosis."

Cleft Lip and Cleft Palate

Several studies specifically evaluated a possible causal relationship between maternal use during pregnancy of antinauseant drugs containing doxylamine succinate and the occurrence of cleft lip and/or palate in infants. A case-control study involved mothers interviewed between March 1976 and June 1980, in 22 participating centers in three regions (Boston, Philadelphia, and Toronto). In this study, Mitchell et al. (Ref. 16) did not find an appreciable increase in the risk of the occurrence of cleft lip and/or cleft palate or of the occurrence of heart defects for infants exposed in utero early in pregnancy to an antinauseant drug containing doxylamine succinate. Infants with birth defects were identified through the review of records of participating hospitals, clinics, and physicians. Mothers of infants with birth defects were interviewed by trained pediatric nurse interviewers. They used a questionnaire to elicit information concerning a great number of factors that could influence the occurrence of birth defects, including possible confounding factors for the specific factors studied (e.g., drug exposure). The interviews included mothers of 98 infants with isolated cleft palate, mothers of 221 infants with cleft lip with or without cleft palate, mothers of 122 infants with selected heart defects (ventricular septal defect, patent ductus arteriosus, atrial septal defect, and coarctation of the aorta), and mothers of 970 infants with malformations other

than those studied that served as controls for the study. The investigators found the following relative risk estimates for infants exposed to the anti-nauseant drug containing doxylamine succinate in utero: for isolated cleft palate, a relative risk estimate of 0.9 with a 95 percent confidence interval of 0.5 to 1.5; for cleft lip with or without cleft palate, a relative risk estimate of 0.6 with a 95 percent confidence interval of 0.4 to 0.8; and for the selected heart defects, a relative risk estimate of 1.0 with a 95 percent confidence interval of 0.6 to 1.6. The investigators' evaluation of possible confounding factors did not demonstrate that any of these factors materially influenced the relative risk estimates found for drug-exposed infants with the birth defects studied.

In England, Golding et al. (Ref. 17) studied 196 index women, i.e., women who had infants with clefts of the lip or palate, and 407 control women (2 controls per index case) that were matched with the index women for age, parity, social class, and year of delivery. The study covered births between 1965 and 1974 and included approximately 14,000 births per year. The investigators found a significant excess ($p < 0.02$) of women who had been prescribed a three-component anti-nauseant drug containing doxylamine succinate, dicyclomine hydrochloride, and pyridoxine hydrochloride in early pregnancy in the index group when compared to the control group. Cases of clefts of lip or palate were ascertained through examination of diagnostic information on home and hospital deliveries, diagnostic details on records of stillbirths and death certificates, details from hospital admission records (usually for cleft repair), details from the malformation register kept by the Oxford Record Linkage study, and case records kept by the M. R. C. Population Genetics Research Unit. Data concerning maternal drug use in early pregnancy were obtained from the notes of attending physicians. The investigators confined their analysis to women presenting with nausea within 69 days of their last menstrual period, because any pathological event that influences the development of cleft lip or palate must take place by the end of the first 9 weeks of gestation. They found no significant differences between index and control women with respect to presenting with nausea during pregnancy, but found a statistically significant excess of index women who were prescribed the three-component anti-nauseant in comparison to all control women who were not prescribed

the drug ($p < 0.02$). The investigators also found a statistically significant excess of index women who had been prescribed the drug in comparison to all other women who had presented with nausea during pregnancy ($p < 0.025$). A matched analysis of the index and control cases yielded a statistically significant excess of index women who had been prescribed the three-component anti-nauseant drug ($p < 0.025$). Analysis of the significant excess of index women who had been prescribed the drug produced a relative risk of 2.88 for the occurrence of cleft lip or cleft palate for infants of mothers who had taken the drug. The investigators found that the mean of the times during gestation at which index women were first prescribed the three-component anti-nauseant drug (7.46 ± 0.37 weeks) was statistically different ($p < 0.025$) from the mean of the times during gestation at which control women were first prescribed the drug (9.29 ± 0.62 weeks). Only 3 of the 12 index women had been prescribed other drugs in addition to the anti-nauseant drug. The investigators concluded that, in view of the lack of consistent agreement in the literature, and in spite of several case reports, the findings of this study alone do not prove the case against the three-component anti-nauseant drug. However, the investigators stated that it is worth questioning whether prescribing the drug for pregnant women with mild nausea and vomiting is advisable.

Heart Defects

Rothman et al. (Ref. 18) evaluated the effect of hormonal exposure before or during pregnancy on the risk of congenital heart disease. A case-control study of 390 mothers of infants with congenital heart disease and 1,254 mothers of normal infants was employed. This study also assessed the cardiovascular teratogenicity of other drugs taken during early pregnancy, including an anti-nauseant drug containing doxylamine succinate, dicyclomine hydrochloride, and pyridoxine hydrochloride. The cases of congenital heart disease studied occurred during the period 1973 to 1975 in Massachusetts. The normal controls were randomly selected from the roster of all Massachusetts births for the same 3-year period of time. Most cases were obtained from the roster of the New England Regional Infant Cardiac Program (NERICP). Other cases were identified by examining death certificate files. Mothers of cases identified through death certificates were interviewed by telephone. Mothers of cases identified through NERICP and controls were mailed questionnaires which inquired

about maternal age, education, reproductive history, contraceptive history, and exposure to tobacco, alcohol, and drugs prior to and during early pregnancy. The proportion of cases with a history of drug exposure was compared with the proportion of controls with a similar history. Based on these data, prevalence ratios were calculated, i.e., the prevalence of heart defects in exposed infants was divided by the prevalence of heart defects in unexposed infants. The data were analyzed for possible confounding variables for factors that strongly correlate with congenital heart disease, i.e., parity, maternal age, educational background, and insulin use. The data were found to be free of confounding by these factors. Accordingly, it was unnecessary to stratify the data for analysis to account for any of these factors. In the case of the anti-nauseant drug containing doxylamine succinate, 24 case mothers reported that they had used the drug, 366 case mothers reported that they had not used the drug, 46 control mothers reported that they had used the drug, and 1,208 control mothers reported that they had not used the drug. Analysis of these data to compare the prevalence of heart defects in drug exposed infants and unexposed infants yielded a prevalence ratio estimate of 1.8 with a 90 percent confidence interval of 1.2 to 2.7 at the $p < 0.01$ level. The investigators described the possible association between the anti-nauseant drug, among other drugs, as "weak." The investigators cautioned that drug exposure information for such drugs was obtained from an open-ended question that would likely be subject to recall bias. In discussing possible associations between hormonal exposure and cardiac defects, the investigators noted that heterogeneity of diagnoses for specific heart defects in exposed cases of defects could be considered to be evidence against an association between exposure and the occurrence of defects. In the case of exposure to the anti-nauseant drug containing doxylamine succinate, the investigators reported five different types of cardiac defects. The numbers of the cases reported for each specific type of defect were evenly distributed over all five types of defects. The investigators also discussed inconsistencies between the results in this study and the results found in other published studies. The investigators concluded that resolution of these discrepancies would require considerably larger studies than those that were published at that time.

Limb Deformities

Other studies investigated the hypothesis that maternal use of an antinauseant drug containing doxylamine succinate is related to the occurrence of limb deformities in infants. Correy and Newman (Ref. 19) analyzed data concerning the occurrence of limb reduction deformities in Tasmania, Australia, during the period 1975 to 1980. Data included forms completed by nurses before mothers were discharged from the hospital that required information concerning congenital abnormalities of the infants. Details concerning maternal use of an antinauseant drug containing doxylamine succinate, dicyclomine hydrochloride, and pyridoxine hydrochloride during pregnancy were obtained from attending physicians of mothers who gave birth to children with congenital anomalies, including limb reduction defects. Data were presented concerning the number of births each year, the number of reported congenital abnormalities, the specifics of 15 cases of limb reduction defects including a history of maternal antinauseant drug use, and the amount of the antinauseant drug distributed each year in Tasmania. The investigators discussed other published studies concerning maternal antinauseant drug use in relation to congenital anomalies and stated that the incidence of limb reduction deformities in Tasmania was 0.03 percent for the time period studied. Based on the evidence presented in this study and a review of the literature, the investigators concluded that ingestion of the antinauseant drug containing doxylamine succinate during pregnancy does not cause limb reduction deformities.

Aselton et al. (Ref. 20) examined drug use during pregnancy and its relationship to serious limb disorders in infants born between January 1980, and December 1981. This study was part of a long-term follow up study of pregnant women and their infants at the Group Health Cooperative of Puget Sound in Seattle. In the cohort of 5,255 women studied, 1,364 (26 percent) obtained one or more prescriptions for an antinauseant drug containing doxylamine succinate. Of these 1,364 women, 556 (41 percent) had two to four prescriptions filled for the antinauseant and 167 (12 percent) had five or more prescriptions filled for the antinauseant. Of the six infants who were born with serious limb disorders, two had syndromes with multiple defects, and the other four had either polydactyly or syndactyly. The mothers of the two infants with multiple defects had

prescriptions filled for the antinauseant drug containing doxylamine succinate; the mothers of the other four infants with limb defects alone had not had prescriptions filled for the drug. The estimate of relative risk for the occurrence of limb defects in infants comparing mothers who had used the drug with mothers who had not used the drug was 1.4 with a 95 percent confidence interval between 0.26 and 7.71. None of the 167 mothers who had obtained five or more prescriptions of the drug containing doxylamine succinate gave birth to infants with limb defects. Using data from a study done by Jick et al. (Ref. 21) (discussed below) for the Group Health Cooperative of Puget Sound, the investigators identified eight infants with serious limb disorders from the offspring of the 6,837 pregnant women in that study that were born between July 1977, and December 1979. Among 2,255 mothers who had prescriptions filled for the antinauseant drug containing doxylamine succinate, 2 (0.9/1,000) had infants with limb disorders; among the 4,582 mothers who did not have prescriptions filled for the drug, 6 (1.3/1,000) had infants with limb disorders. The combined results of the Jick et al. study (Ref. 21) and this study (Ref. 20) yield a relative risk estimate of 0.9 with a 95 percent confidence interval between 0.29 and 2.98 for limb disorders when the antinauseant drug users are compared with nonusers. The investigators concluded that the combined results of these two studies provide evidence against a strong association between the use of the antinauseant drug containing doxylamine succinate in the first trimester of pregnancy and the occurrence of serious limb disorders in infants.

McCredie et al. (Ref. 22) investigated an alleged association between use during pregnancy of an antinauseant drug containing doxylamine succinate, dicyclomine hydrochloride, and pyridoxine hydrochloride and congenital limb defects. The study included 155 mothers with limb-deficient children born during the years 1970 to 1981 and 274 mothers of matched normal children in Australia. Two controls were sought that matched each limb-deficient case for birthdate of the child within 2 months and for equivalent geographical area where mothers lived during the first trimester of their pregnancies. In 119 case-control sets, 2 control children per case were found, and in 36 case-control sets, 1 control child per case was found. Three team doctors interviewed all women studied and recorded data on a standardized questionnaire form

concerning pregnancy history that included details of morning sickness and antinauseant drug use. Morning sickness was reported by 69 percent of the case mothers and 72 percent of the control mothers. Twenty-six percent (429) of all the women studied used the antinauseant drug containing doxylamine succinate in the first trimester of pregnancy. The estimate of relative risk for limb defects in children born to women who had used the antinauseant drug was 1.1 (95 percent confidence limit of 0.8 to 1.5), compared to the estimate of relative risk of 1.0 in children born to women who had not used the drug. In addition, the investigators did not find statistically significant differences in the relative risk estimates reported for analyses to determine if any risk is associated with commencement of use of the drug early in pregnancy or with duration of drug use during pregnancy. The investigators concluded that this study "provides no evidence that [the antinauseant drug containing doxylamine succinate] is implicated in the aetiology of congenital limb defects."

David (Ref. 23) studied the Poland anomaly in infants (a rare unilateral absence of the pectoralis major muscle with an ipsilateral hand defect at birth), and cases of the isolated absence of the pectoralis major muscle in infants at birth, which may be a malformation related to the Poland anomaly. This study was designed to determine whether a causal relationship exists between the occurrence of these malformations in infants and the use during pregnancy of a three-component antinauseant drug containing doxylamine succinate, dicyclomine hydrochloride, and pyridoxine hydrochloride. David examined 46 cases of Poland anomaly and 32 case of the related abnormality which occurred between 1891 and 1977. The investigator noted that a drawback to the study is that it is retrospective, with no control group. He explained that it would be extremely difficult to obtain a control group for cases that spanned 90 years and that the rarity of the defects studied would make a prospective study of a large number of cases impossible. Data concerning maternal use of drugs during pregnancy were obtained from the mothers' hospital antenatal records and by obtaining details of drug prescription from the family doctor. Details of drug ingestion could not be obtained in six cases that occurred before 1924. The three-component antinauseant drug had been prescribed in 2 of the remaining 72 cases. Twenty-six (14 Poland anomaly and 12 isolated pectoralis absence)

cases were conceived before 1958, the year in which the three-component antinauseant drug was introduced into the United Kingdom, and the investigator concluded that these cases could not have a causal relationship to the drug. In addition, the critical period of embryogenesis for the Poland anomaly, and presumably for the absence of the pectoralis major muscle, has been estimated to be 44 to 48 days or 43 to 46 days after conception. In the two cases of birth defects studied where the mother had been prescribed the three-component drug, maternal use of the drug in one case was before the critical period of embryogenesis for the defect. The maternal use of the drug in the other case was after the critical period of embryogenesis for the defect. The investigator concluded that, despite theoretical disadvantages, "in none of the 46 cases of the Poland anomaly or 32 cases of isolated pectoralis absence was there any evidence that [the three-component antinauseant drug] could have caused the defect."

Spina Bifida and Anencephaly

In a case-control study, Hayery et al. (Ref. 24) investigated a five-fold increase in the incidence of the neural tube defects spina bifida and anencephaly during the years 1979 to 1980 in the Antioch-Pittsburg, CA area. The study included 9 cases of neural tube defects and 27 control mothers as well as 8 other cases of neural tube defects and 17 control fathers. The mothers and fathers were evaluated for factors such as place of residence, occupation, drug use, illnesses, and pesticide or chemical exposure. None of the factors evaluated in this study, except fathers' smoking ($p < 0.05$), were associated with the occurrence of neural tube defects. The data evaluated included hospital records, birth and fetal death records, and interviews with parents of neural tube defect cases and the control mothers and fathers. Between March 1979, and November 1980, the investigators identified 10 cases of neural tube defects in an estimated 2,000 births in the Antioch-Pittsburg area during the study period, an incidence of approximately 0.005. Based on a reported annual incidence of approximately 0.001 for California, only two cases of neural tube defects would have been expected in the study population. Three control parents per each case of neural tube defect were randomly selected from patients in the Kaiser-Permanente Medical Care Program. These controls were matched with cases of neural tube defect for the sex of the child, the county of residence for the mother, and for the date of birth

occurring within 1 year of the case child. The investigators evaluated the data in both matched and unmatched statistical analyses. The results of the unmatched analysis were presented for several exposure factors including maternal use during pregnancy of an antinauseant drug containing doxylamine succinate. Two of nine cases (22 percent) of neural tube defects occurred in infants who were exposed to this antinauseant drug in utero during the first trimester of pregnancy, while five of seven controls (15 percent) were exposed to the drug in utero during the first trimester of pregnancy. The difference between drug exposure (22 percent for cases and 15 percent for controls) in the cases and controls was not found to be statistically significant at the $p < 0.05$ level. The investigators noted that the small sample size resulted in problems of low statistical power, i.e., only large odds ratios could be detected at the $p < 0.05$ level. Therefore, the absence of statistically significant results in this study may have been due to a lack of statistical power as well as a lack of association with the factors studied. The investigators concluded that, "whereas it remains necessary to define the possible part that subtle environmental as well as genetic factors may have in the etiology of neural tube defects, it appears possible that the Antioch-Pittsburg cluster occurred by chance."

Absence of Anal, Genital, and Urinary Orifices

Robinson and Tross (Ref. 25) reported five cases of preterm infants (one male and four females) born without anal, genital, and urinary orifices that were identified among 8,241 total births from three counties in northeastern Ohio within a 7.5-month period. The infants were either stillborn or died within hours of delivery. None of the infants displayed any vestige of structures derived from either the embryonic anogenital folds or anal tubercles. The investigators searched for a possible explanation for the occurrence of the malformations studied. Based on cytogenetic and pedigree analysis, the investigators could not identify a genetic mechanism to explain the malformations. However, the malformations studied met the following criteria for the identification of a teratogen: (1) An abrupt increase in the incidence of the anomaly, (2) coincidence of the increased incidence with an environmental change, (3) exposure to the environmental change early in pregnancy yielding infants with the anomaly, and (4) absence of other factors common to all pregnancies yielding an infant with the anomaly. The

investigators suspected the environmental agents doxylamine succinate, dextromethorphan, and acetaminophen as teratogens. Of these agents, only doxylamine succinate was common to all five cases. For this reason, doxylamine succinate was considered the most probable suspected teratogen. In four of the five cases, the mothers took OTC drugs containing doxylamine to treat symptoms of an upper respiratory infection within the first 8 weeks of pregnancy. In the fifth case, the mother took a prescription drug containing doxylamine succinate for nausea and vomiting. The investigators stated that in all five cases, the exposure to doxylamine succinate was within the first 50 days of pregnancy, which is the critical period for initiating the birth defects studied. The authors stated that "with data from only five cases, we are reluctant to make categorical statements about etiology, but the scant number of previous reports of the syndrome [seven reports in the previous 54-year period between 1926 and 1980] and the circumstances of its occurrence in our community warrant further evaluation."

Other Studies

Many studies have evaluated the relationship between maternal use of antinauseant drugs during pregnancy and the occurrence of birth defects in general and the occurrence of a variety of specific birth defects. Cordero et al. (Ref. 26) studied maternal exposure to an antinauseant drug containing doxylamine succinate for possible associations with several major categories of birth defects. However, no associations were found with any of these major categories. Data were obtained from the Metropolitan Atlanta Congenital Defects Program for births between January 1, 1970, and December 31, 1978. Birth defects that were diagnosed in the first year of life were ascertained by staff members of Metropolitan Atlanta Congenital Defects Program through regular visits to obstetric and pediatric wards of hospitals and to secondary and tertiary pediatric units in five central counties of the Atlanta metropolitan area. Data were analysed from 1,231 interviews of parents with infants who had selected defects. Between 1970 and 1978, the selected defects included the neural tube defects anencephaly, spina bifida, encephalocele; cleft lip and/or cleft palate; esophageal atresia; small-bowel atresia; rectal and anal atresia; diaphragmatic hernia; gastroschisis and omphalocele; and Down's syndrome. Between 1973 and 1978, interviews also

included parents of infants with limb reduction defects. Of the mothers interviewed, 117 (9.5 percent) had taken the antinauseant drug containing doxylamine succinate in the first trimester of pregnancy. There were not statistically significant differences in exposure to the antinauseant drug among any of the 12 birth defect categories analyzed. The rate of first trimester exposure to the antinauseant drug containing doxylamine succinate for each birth defect was compared with the rate of such drug exposure for a control group composed of infants with birth defects other than the birth defect being evaluated. Odds ratios for the occurrence of birth defects in infants whose mothers had taken the antinauseant drug containing doxylamine succinate in the first trimester of pregnancy were tested for statistical significance for each defect category. The authors stated that among the subgroups of limb defects, only the amniotic bands complex had a significantly increased first trimester exposure to the antinauseant drug (odds ratio 3.88, $p=0.015$). However, when the data were stratified by two time periods of drug exposure, the amniotic bands complex did not show a statistical association with drug exposure. The authors concluded that the data were insufficient to demonstrate a causal effect between drug exposure and the occurrence of the amniotic band complex, but that further studies are indicated to determine if there is a causal relationship. Stratification by two time periods of drug exposure yielded a statistically significant association between the occurrence of encephalocele and exposure to a two-component antinauseant drug product containing doxylamine succinate and pyridoxine hydrochloride ($p=0.038$). Also, there was a statistically significant association between esophageal atresia and exposure to a three-component antinauseant drug containing doxylamine succinate, dicyclomine hydrochloride, and pyridoxine hydrochloride ($p=0.044$). The authors concluded, however, that it seems unlikely that a causal relationship exists between first trimester exposure to these prescription drugs and the occurrence of encephalocele for the following reasons: (1) No other reports suggest such an association, (2) the association was found only for the two-component drug and not for the three-component drug, and (3) although a significant increase in the population rate of encephalocele should have been observed following the introduction of the two-component drug and

discontinued use of the three-component drug in 1977, the data did not show such an increase in the rate of occurrence of encephalocele. The authors stated that the association between the three-component drug and the occurrence of esophageal atresia is weak, but that they did not find, however, any confounding factors that would explain the association. The authors concluded that further studies would be required to evaluate this finding. In conclusion, the authors stated that "in our opinion, these data do not suggest that [either one of the antinauseant drugs studied that contain doxylamine succinate] is causally associated with the occurrence of the birth defect categories that we studied. If any causal association does exist between first trimester exposure to [the antinauseant drugs studied that contain doxylamine succinate] and the three particular defects amniotic bands, encephalocele, and esophageal atresia, the actual risks seem to be extremely small. Since it is impossible to prove any agent safe, our study should remind physicians that the potential risk of drugs during pregnancy should be weighed against the potential benefits that they may have."

Cordero and Oakley (Ref. 27) discussed epidemiologic methodologies and their application to studies concerning relationships between the occurrence of birth defects and exposure to drugs during pregnancy. They reviewed several studies concerning use during pregnancy of an antinauseant drug containing doxylamine succinate. Based on the results of several cohort studies (refs. 6, 8, 21, 28, 29, 31, and 32) concerning possible associations between the antinauseant drug and the occurrence of birth defects, they concluded that it is possible to exclude a risk of birth defects of over 1.2 per 1,000, and stated that "if there is a risk in the use of that drug, it should be less than 0.12 percent, which is significantly less than the 2-3 percent risk that any pregnancy has just by chance for serious malformations." The authors also presented a preliminary unpublished analysis by Martinez-Frias et al. (Ref. 40) in a case-control analysis of the Spanish Collaborative Study of Congenital Malformations that showed a group of 53 cases of diaphragmatic hernias. Five cases (9.4 percent) in this group had been exposed in utero to an antinauseant drug containing doxylamine succinate, dicyclomine hydrochloride, and pyridoxine hydrochloride. Of the 4,965 infants in the control group who were not born with diaphragmatic hernias, 633 infants (12.7 percent) had been exposed in utero to

the drug. The difference between the two groups with respect to the proportion of infants who had been exposed to the antinauseant drug was not statistically significant.

Jick et al. (Ref. 21) found no strong associations between any of the drugs commonly used during pregnancy, including an antinauseant drug product containing doxylamine succinate, and the congenital disorders studied. The investigators evaluated computerized data that included all prescriptions the mothers had filled during the first trimester of pregnancy and congenital disorders diagnosed at birth, excluding those that were subsequently diagnosed as normal. The subjects were women and their infants in the Group Health Cooperative of Puget Sound in Seattle. The study covered births between July 1, 1977, and December 31, 1979. The data analyzed included 6,837 pregnancies that produced live births, 80 (1.2 percent) of which resulted in infants with the following congenital disorders: limb reduction deformity (4), other limb deformities (4), cleft lip/palate (5), rectal atresia (5), esophageal atresia (1), congenital heart disease (15), central nervous system disorders (3), undescended testicle (22), chromosome disorders (8), congenital cataract (1), choanal atresia (2), thyroglossal sinus (1), congenital ureteral obstruction (2), Potter's syndrome (1), familial Saethre-Chotzes syndrome (1), congenital eperlides (1), medulloblastoma (1), insulin-secreting tumor (1), and hypospadias (2). Disorders, such as pyloric stenosis, that were diagnosed subsequent to the hospital admission for childbirth were excluded from analysis in this study. Infants of mothers who were considered exposed to a drug if the mother had one or more prescriptions for the drug filled. Prescriptions for a drug product containing doxylamine succinate and pyridoxine hydrochloride were filled for 33 percent of the 6,837 women studied. The prevalence of all disorders among drug exposed infants was found to be 24 per 2,255 live births (1.1 percent), which was closely similar to the prevalence of all disorders among infants who were not exposed to this drug, i.e., 56 disorders per 4,582 live births (1.2 percent). The investigators also evaluated the prevalence of particular disorders in infants exposed to the drug containing doxylamine succinate and pyridoxine hydrochloride. Only in the case of gastrointestinal atresia was the prevalence high for drug exposed infants. However, the 95 percent lower confidence bound (limit) found for this association was below unity, and there was little association

with the time of drug exposure during pregnancy and the occurrence of the disorder. Also, there was no positive correlation between increasing numbers of prescriptions filled for the drug and the occurrence of the disorder.

Aselton et al. (Ref. 33) updated the study by Jick et al. (Ref. 21, discussed above) concerning possible associations between any of the drugs commonly used during pregnancy and the major congenital disorders studied. This study included all live births of 6,509 mothers in the Group Health Cooperative of Puget Sound in Seattle between January 1, 1980, and June 30, 1982. The same study methods reported in the Jick et al. study (Ref. 21) were used in this study. Of the 6,509 women studied, 105 (1.6 percent) delivered infants with congenital disorders, and 1,580 (23 percent) had at least one prescription filled for an anti-nauseant drug containing doxylamine succinate. The investigators stated that the prevalence of any disorder among infants whose mothers had at least one prescription filled for the anti-nauseant drug containing doxylamine succinate (30 infants with disorders among 1,580 infants; 1.9 percent) was slightly higher than that of infants whose mothers had not had a prescription filled for the drug (75 infants with disorders among 4,929 infants; 1.5 percent). This factor resulted in an estimated risk ratio of 1.25, with a 95 percent confidence interval of 0.8 to 1.9, for infants whose mothers had at least one prescription filled for the drug. The investigators found no difference in the prevalence of disorders when they evaluated the gestational time when mothers had prescriptions filled for the anti-nauseant drug or when they evaluated how many prescriptions were filled. They found no strong positive association of the occurrence of the congenital disorders studied with maternal use of any of the drugs studied. When they evaluated the combined data from this study and the Jick et al. study (Ref. 21) covering experience over a 5-year period, they found that the rate of congenital disorders diagnosed at birth among infants born to mothers who had had at least one prescription filled for the anti-nauseant drug containing doxylamine succinate (14 per 1,000 births) was identical to that of infants born to mothers who had not had prescriptions filled for the drug (14 per 1,000 births). The investigators concluded that "although the data presented on most of the drugs in this study are insufficient to rule out a modest association, they do rule out a strong association with many commonly used drugs and the generally serious

congenital defects included in this evaluation."

Michaelis et al. (Ref. 7) did a cohort study in West Germany that included 13,643 pregnancies occurring between 1964 and 1976. This study looked for the possible influence on pregnancy and child development of various factors, including the use of antiemetic drugs and sex hormones in early pregnancy. The investigators found no evidence of increased risk for major malformations in infants following the use of the antiemetic drugs studied or with the use of progesterone during early pregnancy. Data concerning drug use were collected in the form of diaries kept by almost 15,000 pregnant women recruited for the study and from medical records kept by the attending physicians. The diary information included exposure to drugs and other chemical agents such as detergents, insecticides, and fertilizers. Other factors considered were the daily work load of the women and the occurrence during pregnancy of diseases, accidents, or surgical operations. At each visit by the women, the attending physicians checked the diary information, particularly with respect to what drugs were prescribed for and ingested by the women. Data were also collected from detailed medical records concerning the course of the delivery of the infants. Data concerning aborted fetuses were collected when possible and included histological and chromosomal examinations of the fetus. Data concerning the children born consisted of information collected during examinations of the children immediately after birth; within 3 to 5 days of birth; at the ages: 6 weeks, 40 weeks, 18 months, 36 months; and for some children at 6 years. Detailed information was collected concerning the occurrence of diseases in the children and diaries were kept by the mothers regarding the physical and intellectual development of their children. All congenital malformations that occurred in the infants studied were judged by an expert committee (of pediatricians) on human genetics who classified the malformations as major, minor, or other abnormalities. The investigators used computers to analyze an average of 4,500 different data items per pregnancy for 13,643 pregnancies. They evaluated the frequency of the occurrence of malformations in infants of mothers who had taken specific drugs during the first trimester of pregnancy. That frequency was compared to the frequency of the occurrence of malformations in infants in a matched control group selected from the total

cohort of women and infants studied that had not been exposed to the drug. The control women were matched with the drug exposed group for maternal age, parity, and marital status. An anti-nauseant drug containing doxylamine succinate, dicyclonine hydrochloride, and pyridoxine hydrochloride was taken by 1,001 women in the study group. Of these 1,001 pregnancies, 50 (5 percent) resulted in abortions and 20 (2 percent) resulted in the birth of an infant with major congenital malformations. Of the 1,001 pregnancies, including 18 that resulted in infants with major malformations, 874 could be matched with control pregnancies for analysis. Nineteen infants with major malformations were born to mothers in the control group. Analysis of the data resulted in an odds ratio of 0.95 with 90 percent confidence limits of 0.52 to 1.73 for the occurrence of major malformations in infants born to mothers who had taken the anti-nauseant drug containing doxylamine succinate during the first trimester of pregnancy. The malformations that occurred in infants exposed to this specific drug showed no common characteristics. An analysis was done of the impact of other factors for which data were collected in order to detect possible systematic selection factors that might have been introduced by selecting the matched controls. This analysis showed both groups to be comparable with respect to the factors which could not be controlled by matching. The only differences found were that women who used the drug containing doxylamine succinate practiced contraception prior to becoming pregnant and women in the control group who had not taken this particular drug smoked cigarettes more frequently.

In a study conducted in England, Smithells and Sheppard (Ref. 28) found no evidence to suggest that a three-component anti-nauseant drug containing doxylamine succinate, dicyclonine hydrochloride, and pyridoxine hydrochloride is teratogenic. The study included 2,298 pregnant women from either the Leeds area during the period between August 1974, and July 1975, or the Liverpool area during the period between June 1974 to July 1975. Data were obtained from the Prescription Pricing Authority, birth notification records, and hospital maternity records or midwives' records. Of the 2,298 pregnancies studied, there were 2,261 live infants (including 19 sets of live twins), 23 stillbirths and 1 stillborn twin (24 infants that did not survive birth), 21 spontaneous abortions, 1 therapeutic

abortion, and 1 maternal death. The investigators evaluated the estimated gestational age of the fetus at the time it was first exposed in utero to the anti-nauseant drug. They compared the incidence of the occurrence of major defects in infants first exposed to the drug at different estimated gestational ages. They found, for major defects, an incidence of 1.8 percent in 990 infants first exposed to the drug at approximately 1 to 8 weeks gestation, an incidence of 1.5 percent in 1,374 infants exposed at approximately 1 to 10 weeks gestation, and an incidence of 1.7 percent in 1,622 infants exposed at approximately 1 to 12 weeks gestation. For infants exposed after approximately 10 weeks gestation, the incidence of major defects was 1.5 percent; for infants exposed after approximately 12 weeks gestation, the incidence of major defects was 1.2 percent; and for infants exposed after approximately 14 weeks gestation, the incidence of major defects was 1.2 percent. When the investigators compared the incidence of major defects for births to mothers who had a prescription filled for the three-component drug with the incidence of major defects for all births in the study, they found (1) in Liverpool, an incidence of 2.2 percent for all births and an incidence of 2.1 percent for drug-exposed births; (2) in Leeds, an incidence of 1.5 percent for all births and an incidence of 1.3 percent for drug-exposed births; and (3) an overall incidence of 1.8 percent for all births studied and an incidence of 1.5 percent for all drug-exposed births studied. The incidence of major defects found for infants of mothers who had prescriptions filled for the three-component drug during approximately the first 10 weeks of gestation was the same as that found for infants of mothers who had prescriptions filled for the drug after the first 10 weeks of gestation, i.e., 1.5 percent for both groups. The investigators found a wide spread of common anomalies, rather than a characteristic malformation or group of malformations in infants of mothers who had filled prescriptions for the three-component drug. The investigators concluded that "this study provides substantial evidence that [the anti-nauseant drug containing doxylamine succinate] is not teratogenic in man."

In a prospective study to investigate maternal characteristics and habits during pregnancy and their impact on fetal development, Morelock et al. (Ref. 34) studied 1,690 mother/infant pairs, between February 1977, and October 1979, at the Boston City Hospital. The

study group included 375 mothers who had indicated in interviews that they had used a prescription drug containing doxylamine succinate for nausea during pregnancy. In multivariate analyses that examined infant birth weight, birth length, head circumference at birth, gestational age at birth, and congenital malformations as dependent variables, the investigators found no associations between maternal use of the prescription anti-nauseant drug containing doxylamine succinate and adverse fetal outcome. Shortly after delivery, 1,962 mothers were interviewed about a variety of health behaviors associated with infant outcome within the medical literature. The infants of 272 of the women who were interviewed were not examined for the purposes of this study. Infants of 1,690 of the interviewed mothers were examined to assess growth, neurologic, and morphologic parameters by one of four pediatricians. These infants were classified according to birth weight, length, head circumference, gestational age, and the number of major or minor congenital malformations they exhibited. Infants were classified in two groups, i.e., (1) infants with three or more minor abnormalities and those with one or more major abnormalities that are life-threatening or that require surgery or (2) infants with abnormalities, such as skeletal abnormalities, limb deformities, cleft-lip or palate, and cardiac defects, that had been attributed in the literature to the use during pregnancy of the anti-nauseant drug. Eight hundred twenty-four infants whose mothers were not interviewed were also examined and classified as described above. The infants of mothers interviewed and of mothers not interviewed did not differ in birth weight, length, gestational age, head circumference, or proportion exhibiting any congenital abnormalities or abnormalities associated in the literature with use of the anti-nauseant drug. Of the 1,690 mothers who were interviewed and whose infants were examined, 375 (22.2 percent) reported taking the anti-nauseant drug during pregnancy, and 21.2 percent of the 272 women who were interviewed but whose infants were not examined reported taking the drug during pregnancy. The investigators used discriminant analysis to explore whether mothers who reported using the anti-nauseant drug during pregnancy disproportionately exhibited behaviors or characteristics (e.g., complications and characteristics of pregnancy, environmental exposures, demographic, or reproductive characteristics) that

would subsequently put their infants at risk. The investigators found that women who reported using the drug during pregnancy tended to be older, to consume more alcohol during pregnancy, to be more frequently x-rayed, and to smoke fewer cigarettes than women who did not report using the drug. The investigators stated that these factors have been associated with elevated malformation rates and lower birth weights for infants. They added that smoking and alcohol use during pregnancy had been reported to relate to shorter gestational age of the infant at birth. The investigators accounted for these confounders in their analysis of the data. Univariate comparisons showed that the mean birth weight of infants whose mothers had used the anti-nauseant drug during pregnancy was higher than the mean birth weight of infants whose mothers had not used the drug. Univariate comparisons did not show differences between infants whose mothers had used the drug and infants whose mothers had not used the drug with respect to birth length, head circumference, gestational age, 1- or 5-minute Apgar scores; infant medical illnesses at birth; distribution of male and female infants; or distribution of malformations in the infants. Because the investigators did not find sufficient numbers of cases of cleft lip or palate and limb deformities, these two categories of malformations were not analysed separately, but were included in the overall analysis of all abnormalities in infants attributed in the literature to maternal use of the anti-nauseant drug during pregnancy. The investigators concluded that the converging evidence from this and other studies strongly suggests that the use of the anti-nauseant drug containing doxylamine succinate during pregnancy does not adversely affect infant outcome.

In Northern Ireland, Harron, Griffiths, and Shank (Ref. 35) investigated the alleged association between fetal abnormalities and the use during pregnancy of an anti-nauseant drug containing doxylamine succinate, dicyclomine hydrochloride, and pyridoxine hydrochloride. During the study period, the total number of births in Northern Ireland fell from 33,778 births per year in 1966 to 25,747 births per year in 1977 and then increased to 26,483 in 1978. The incidence of infants born with cleft lip, cleft palate, limb reduction deformities, and defects of the heart and great vessels also fell during the period 1966 to 1978 and increased in 1977 and 1978. During the same time period, the number of prescriptions for

the anti-nauseant drug increased more than four-fold from 3,841 prescriptions in 1966 to 15,954 prescriptions in 1978. When the overall incidence of specific congenital malformations was compared with use of the anti-nauseant drug during pregnancy, the incidence of these malformations over the years studied did not appear to change while the number of prescriptions for the drug per 100 births rose more than five-fold from 11.4 in 1966 to 60.2 in 1978. Data concerning all births (live and stillborn) and the number of tablets of the anti-nauseant drug prescribed were obtained from governmental records. The investigators stated that the results of the study suggest that there is no relationship between congenital malformations and the use of the anti-nauseant drug containing doxylamine succinate during pregnancy.

During the mid-1960's, Fleming, Knox, and Crombie (Ref. 6) followed prospectively 22,977 pregnant women in Scotland and England for the incidence of malformations in the infants born to these women. The investigators analyzed data collected in two studies, an English study covering 8,293 pregnancies and a Scottish study covering 14,684 pregnancies. Of the 22,977 pregnancies, 620 women were prescribed an anti-nauseant drug containing doxylamine succinate, dicyclomine hydrochloride, and pyridoxine hydrochloride during the first 13 weeks of pregnancy. The investigators defined malformation as "a malformation evident at birth or within 6 weeks in either a live or stillborn infant, which could be diagnosed unequivocally excluding skin malformation." Of the 620 women who were prescribed the drug, 589 (95 percent) delivered normal infants, 8 (1.3 percent) delivered malformed infants, and 23 (3.7 percent) had other pregnancy outcomes. Of the 22,357 women who were not prescribed the drug, 445 (2.0 percent) delivered malformed infants. For all abnormal birth outcomes, 5.0 percent involved maternal use of the anti-nauseant drug and 5.4 percent did not involve maternal use of the drug. The investigators stated that "in these studies there was neither a concentration of specific abnormalities nor any particular concentration of exposure period [for the anti-nauseant drug containing doxylamine succinate] among the women with abnormal outcomes" and concluded that the anti-nauseant drug was not specifically incriminated as a cause of malformations in infants exposed to the drug during pregnancy.

In a large, prospective, observational study, Milkovich and Van Den Berg (Ref. 8) evaluated the teratogenic potential of several anti-nauseant drugs, including a drug that contains doxylamine succinate, prescribed during the first 84 days of pregnancy. They found no association between maternal use of the drug containing doxylamine succinate and teratogenicity. Data concerning pregnancy, drug prescription, delivery, and child health and development were obtained for almost 100 percent of the pregnant women who reported for prenatal care at the Kaiser Health Plan's East San Francisco Bay Area medical facilities during the years of late 1959 to 1966. The study included 11,481 single pregnancies. Fifty-eight percent (6,693) of the women studied complained of nausea and vomiting during pregnancy. For 16.5 percent of the women (1,900), the physician stated in the records that the women did not suffer from nausea and vomiting. For 25 percent of the women (2,888), no indication of the presence or absence of nausea or vomiting could be found in the records. For women who were prescribed drugs for nausea and vomiting and those who were not prescribed drugs for these conditions, the distributions of maternal age, race, parity, and the proportion of primigravidas, among other variables, were almost identical. Only severe congenital anomalies (i.e., anomalies that are hazardous or, if not corrected, would impair the child's development or well being, or both) of the infants born were considered in the analysis. In addition, perinatal mortality rates, defined as fetal deaths at 20 or more weeks' gestation, and neonatal deaths were analyzed. The investigators found that for the children of women who had been prescribed the anti-nauseant drug containing doxylamine succinate, the severe congenital anomaly rates were (1) 0.8 percent at 1 month of age compared to a rate of 1.5 percent for children of mothers who were not prescribed any drugs, (2) 1.6 percent at 1 year of age compared to a rate of 2.2 percent for children of mothers who were not prescribed any drugs, and (3) 2.2 percent at 5 years of age compared to a rate of 3.2 percent for children of mothers who were not prescribed any drugs. The perinatal mortality rates for infants of mothers who had been prescribed anti-nauseant drugs, including the drug containing doxylamine succinate, and the perinatal mortality rates for infants of mothers who had not been prescribed anti-nauseant drugs were quite similar, i.e., 27.8 and 32.1 per 1,000 births respectively. None of the mortality rates for specific drugs studied

differed significantly from the no-drug-prescribed group at the $p < 0.05$ level. A comparison of the combined rates for severe congenital anomalies and perinatal death found practically identical rates for the group of infants whose mothers had been prescribed anti-nauseant drugs and the group of infants whose mothers had not been prescribed such drugs, i.e., 60.1 and 60.2 per 1,000 births, respectively. The investigators stated that this study, supported by other independent studies, leads to the conclusion that, among other drugs, the anti-nauseant drug containing doxylamine succinate when taken in doses recommended for pregnant women is not teratogenic.

In a prospective study of 50,282 pregnant women and their offspring, Shapiro et al. (Ref. 36) compared the mean birth weight, perinatal mortality rates, and congenital malformation rates for infants of women who used anti-nauseant drugs containing doxylamine succinate and/or dicyclomine hydrochloride during the first 4 lunar months of pregnancy and the mean birth weight, perinatal mortality rates, and congenital malformation rates for infants of women who had not used anti-nauseant drugs containing the above ingredients. The investigators also obtained data concerning the intelligence quotient scores at 4 years of age for 28,353 of the children in the study group and compared the scores of children who were exposed to the anti-nauseant drugs in utero and those who were not exposed in utero to the drugs. Data were obtained from the Collaborative Perinatal Project. Extensive information on drugs taken during pregnancy, maternal illnesses, complications of pregnancy, and other factors were collected prior to the birth of the child. Drug use information was recorded at each mother's antenatal visit to her physician. Heavy exposure to the anti-nauseant drugs studied was defined as a drug taken by the mother for at least 8 days during one or more of the first 4 lunar months of pregnancy. The statistical analyses of the data collected were controlled for many possibly confounding factors such as maternal age, maternal illnesses such as diabetes, complications of pregnancy, genetic factors, race, socioeconomic status, marital status, birth order, and educational status of the mother. The analysis of congenital malformations showed no statistically significant differences in the relative risk for the occurrence of congenital malformations in general or for the occurrence of the specific congenital malformations

studied for 509 children "heavily exposed" in utero to the drugs studied, 660 children "intermediately exposed" in utero to the drugs studied, and for 49,113 children who were not exposed in utero to the drugs studied. The investigators found no statistically significant differences in the perinatal mortality rates for 1,403 infants who were exposed in utero to doxylamine succinate and for 39,934 infants who were not exposed in utero to doxylamine succinate. Likewise, no statistically significant differences in mean birth weight were found among drug-exposed and unexposed infants when the data were analyzed to take ethnic group and socioeconomic status into consideration. An analysis of the intelligence quotient scores of many of the children studied at 4 years of age found no statistically significant differences among one group of 80 children "heavily exposed" in utero to doxylamine succinate, another group of 837 children "intermediately exposed" to this drug, and another group of 27,441 children who were not exposed to the drug in utero. The investigators concluded that, although it is rarely possible in studies of this type to completely rule out some teratogenic effect, they found no evidence that the antinauseant drugs studied, including doxylamine succinate, are harmful to the fetus.

Using information from the same data base (Collaborative Perinatal Project) used in the Shapiro et al. study (Ref. 36) described above, Heinonen, Slone, and Shapiro (Ref. 29) presented data concerning the occurrence of birth defects in relation to exposure during the first 4 months of pregnancy to antinauseant, antihistamine, and phenothiazine drug products for 50,282 mother-child pairs that included 3,248 malformed children. Relative risks for the occurrence of malformations were presented as crude values, values standardized for hospital variability, and values standardized for the mother's ethnic group and for survival of the child. For mothers who ingested doxylamine succinate during the first 4 lunar months of pregnancy, the investigators found, for the occurrence of malformed infants, a crude relative risk of 1.05, a hospital-standardized relative risk of 0.96, and a relative risk standardized for survival of the child and race of the mother of 1.06. Standardized relative risks (SRR) with 95 percent confidence limits that took into account potential confounding variables were presented for classes of malformations showing uniform rates by hospital in relation to doxylamine

succinate used in the first 4 lunar months by 1,169 pregnant women. For all malformations, the SRR was 1.07 with a 95 percent confidence interval of 0.83 to 1.37; for major malformations, the SRR was 1.06 with a 95 percent confidence interval of 0.78 to 1.45; and for minor malformations, the SRR was 1.37 with a 95 percent confidence interval of 0.98 to 1.93. The highest SRR was 1.68 (95 percent confidence interval of 0.73 to 3.28) for polydactyly in Blacks based on drugs used by 386 Blacks included in the study. No association was found between the ingestion of doxylamine succinate during the first 4 lunar months of pregnancy either with major malformations or with the overall group of malformations. The investigators concluded that, "on the basis of substantial numbers, there was no evidence to suggest that exposure to antihistamines, antinauseants, or to phenothiazines was related to malformations overall, or to large categories of major or minor malformations."

Gibson et al. (Ref. 37) conducted a prospective study of pregnant women attending the Queen Victoria Hospital (6,476 women) and the Obstetric Department of the Queen Victoria Hospital (1,180 women) in Adelaide, Australia. This study evaluated the outcome of pregnancy against exposure to an antinauseant drug containing doxylamine succinate, dicyclomine hydrochloride, and pyridoxine hydrochloride. Each woman was interviewed after birth and at her first antenatal visit to her physician. A wide range of information was collected using a questionnaire that included maternal age; parity; residential area; personal and family medical history; occupation; diet; consumption of alcohol, tobacco, cannabis; other nontherapeutic drugs and therapeutic drugs; exposure to chemicals; and other behavioral and environmental factors. The study population included 5,771 (76.1 percent) women who did not use the antinauseant drug during pregnancy, 1,685 (22.2 percent) women who used the drug during the first trimester of pregnancy, and 132 (1.7 percent) women who used the antinauseant drug after the first trimester of pregnancy. Data analyses compared pregnancy outcomes for the 5,771 women who did not use the antinauseant drug and the 1,685 women who used the drug during the first trimester of pregnancy. Other than anomalies of the male genital tract, analyses for differences in the risk for the occurrence of congenital anomalies that were uncontrolled for possible confounding factors and analyses that

were controlled for possible confounding factors showed no significant differences between children whose mothers had used the antinauseant drug during the first trimester of pregnancy and children whose mothers had not used the drug during pregnancy. The investigators concluded that the study provided no evidence that the use of the antinauseant drug containing doxylamine succinate during the first trimester of pregnancy increases the risk of congenital anomalies either of the cardiovascular system or of the limbs. The multivariate analyses indicated a possible real effect of maternal use of the antinauseant drug in increasing the risks of the occurrence of genital tract anomalies. However, the investigators stressed that a data analysis of the kind performed for this study entails, many different comparisons, thereby increasing the probability that some apparently "significant" differences will emerge as a result of chance alone. The investigators stated that routine statistical significance testing should therefore not be used as a primary criterion in drawing conclusions.

In England, Greenberg et al. (Ref. 38) studied drug use during the first trimester of pregnancy in 836 mothers of congenitally malformed infants and in an equal number of control mothers of normal babies. The study considered possible associations between drug use and subsequent birth of a malformed infant. Cases of infants born with neural tube defects, oral clefts, limb deformities, or other malformations were identified from reports to the Office of Population Censuses and Surveys. The children's general practitioners were contacted. If willing, the physicians were interviewed by a medical field officer to obtain data concerning antenatal, personal, and family history as well as drugs prescribed during the first trimester of pregnancy. For each abnormal "case" baby, similar information was obtained from a mother of a normal "control" baby born within 3 months of the date of birth of the abnormal "case" baby. This study included 836 case-control pairs born in 1969, 1972, or 1973. An antiemetic drug had been prescribed for 178 mothers of control babies and for 157 mothers of case babies; this difference was not significant. Doxylamine succinate was prescribed for both case and control mothers for 13 case-control pairs, for the case mother only for 63 case-control pairs, for the control mother only for 75 case-control pairs, and for neither the case mother nor the control mother for 685 case-

control pairs. The investigators found no evidence that drugs containing doxylamine succinate are teratogenic for the congenital malformations studied.

In a retrospective analysis of drugs ingested in the first trimester of pregnancy in 7,933 consecutive deliveries between 1953 and 1975 in patients in a private practice, Newman, Correy, and Dudgeon (Ref. 30) found no associations between particular congenital abnormalities and particular drugs or groups of drugs studied. However, the investigators did find a twofold increase in congenital abnormalities in patients who had taken drugs of one kind or another during the first trimester of pregnancy. Data were obtained from the records of patients with pregnancies of at least 20 weeks' duration. Data collected included information concerning minor and major anomalies apparent at birth and drugs ingested during the first trimester. Data were analyzed to determine the number and type of congenital anomalies and their relation to drug usage as well as to determine the number of drugs used and their relation to the type and number of congenital anomalies present. Mothers who had a positive history of some type of drug use during the first trimester of pregnancy gave birth to 2,516 babies including 35 infants with malformations, 24 with major anomalies, and 11 with minor anomalies. Mothers who had a negative history for drug use of any kind gave birth to 5,417 babies including 41 infants with malformations, 32 with major anomalies, and 9 with minor anomalies. The observed incidence of anomalies in infants of mothers who used at least one drug was 1.39 percent and the observed incidence of anomalies in infants of mothers who did not use drugs was 0.76 percent. The difference in the observed incidences of anomalies for these two groups was significant at the $p < 0.01$ level. However, analysis of the data did not demonstrate a constant relationship between any particular abnormality and maternal ingestion of any particular drug (including the antinauseant drug containing doxylamine succinate) or between any drug or pharmacologic group of drugs (including antiemetics) and any particular abnormality. The investigators concluded that, while no particular drug was implicated as a teratogen in this study, it is significant that twice the incidence of congenital abnormalities occurred in infants of mothers with a positive history of the use of one or more drugs during the first trimester of pregnancy compared to the incidence of abnormalities in infants of

mothers with a negative history of any drug use during the first trimester of pregnancy.

In Germany, Michaelis et al. (Ref. 31) evaluated the possible teratogenic effects of maternal use of an antinauseant drug containing doxylamine succinate, dicyclomine hydrochloride, and pyridoxine hydrochloride during the first 12 weeks of pregnancy in a prospective study of 13,645 pregnancies. Data were obtained from a prospective study series on the course of pregnancy and child development. The study included 13,645 pregnancies. The mothers were seen by a physician every 4 weeks during pregnancy and these mothers filled out daily diary cards that covered a wide range of factors that could exert an effect on the course of pregnancy and child development, including information concerning maternal drug usage. Maternal drug use was also documented by the attending physician. Of the 13,645 pregnancies, the antinauseant drug containing doxylamine succinate was used by the mother in 1,001 cases during the first 12 weeks of pregnancy and 20 severe malformations (2 percent) occurred in infants born to these mothers. In comparison, 175 severe malformations (1.4 percent) occurred in infants of the 12,644 mothers who did not use the drug during the first 12 weeks of pregnancy. The difference, i.e., 2 percent compared to 1.4 percent, in the incidence of severe malformations in these two groups of infants was not statistically significant. Further analysis of the data yielded a risk ratio of 1.37 with a 90 percent confidence interval of 0.89 to 2.06 for the incidence of severe malformations in infants of mothers who had used the antinauseant drug compared to infants of mothers who had not used the drug. In addition, the malformations observed were very heterogeneous, so that specific types of abnormalities could not be defined for the two groups of infants evaluated. The investigators found no significant differences between the incidence of malformations for groups of infants whose mothers had ingested other antinauseant drugs during pregnancy and for groups of infants whose mothers had not ingested the drugs. A matched-pairs analysis was done of the data where mothers who had used the antinauseant drug containing doxylamine succinate were matched with mothers who had not used the drug with respect to maternal age, parity, number of previous abortions, and the clinic that provided maternal care. The investigators reevaluated the risk ratio for the incidence of severe

malformations in infants whose mothers had used the antinauseant drug containing doxylamine succinate during the first 12 weeks of pregnancy. The study population was divided into two subgroups, one group of 7,870 pregnancies that had been evaluated in an earlier interim publication and another group of 5,775 additional pregnancies evaluated in this study. Matching of pregnancies in the two subgroups resulted in 406 pairs in one group and 468 pairs in the other group. A combined analysis of these two sets of matched pairs yielded a risk ratio of 0.95 with a 90 percent confidence interval of 0.52 to 1.73. The investigators stated that evaluation of the 13,645 pregnancies studied prospectively yielded no grounds for concluding that ingestion of the antinauseant drug containing doxylamine succinate during pregnancy led to an elevated background risk of malformations in infants.

In a case-control study, Bunde and Bowles (Ref. 32) compared the incidence of congenital anomalies in infants who were exposed in utero to an antinauseant drug containing doxylamine succinate with the incidence of congenital anomalies in infants who were not exposed in utero to the drug. The investigators did not find a significant difference in the incidence of abnormalities between drug exposed and unexposed infants. Mothers who had used the antinauseant drug during pregnancy were matched with mothers who had not used the drug with respect to the time of pregnancy, the same physician, and the same hospital. The study involved 21 physicians known to prescribe the antinauseant drug for pregnant patients. Data were obtained from report forms filled out by the physicians that contained information concerning the time and amount of antinauseant drug use by the patient, other drug use during pregnancy, maternal age, length of gestation, maternal illnesses during pregnancy, and condition of the infant at birth. The report form also contained the same information concerning the matched control patient, i.e., "the next previous delivery not taking [the antinauseant drug]." Over approximately 6 years, data concerning 2,218 matched pairs of mothers were reported by the physicians. Of the 32 congenital abnormalities reported for infants of all mothers studied, 21 abnormalities occurred in infants of control mothers and 11 occurred in infants of mothers who had used the antinauseant drug. This difference in the occurrence of abnormalities for drug

exposed and unexposed infants was not significant ($p < 0.10$).

Clark and Clayton (Ref. 39) found no significant differences in maternal use of an anti-nauseant drug containing doxylamine succinate, dicyclomine hydrochloride, and pyridoxine hydrochloride between 788 cases of perinatal death and 788 controls consisting of the first live births that immediately followed the occurrence of the perinatal death at the same obstetric unit. The study included perinatal deaths and live births in Leicestershire, England, during the period 1976 to 1979. Maternal drug use was ascertained through interviews of the mothers. Of the mothers of infants who died, 9.9 percent reported use of the anti-nauseant drug. Of the mothers of infants who lived, 9.4 percent reported use of the drug.

At the 1986 Teratology Society meeting, Rosa (Ref. 41) discussed a study that examined estimated relative risks for spontaneous abortions and live born defects in pregnancy cohorts for each of 510 generically identified drugs, which included doxylamine succinate. The data were obtained from a computerized data base (Michigan Medicaid) on approximately 35,000 annual pregnancies since 1980 and included 104,339 women. A total of 6,564 children ages 0 to 4 years with suspected birth defect diagnoses were linked to the women. Suspected birth defects occurred in 457 of the children born to 5,995 of the mothers who received an anti-nauseant drug containing doxylamine succinate 300 to 180 days before delivery (i.e., in the first trimester). A relative risk estimate of 1.2, with 95 percent confidence limits of 1.1 to 1.4, was found for all birth defects for children whose mothers had received the anti-nauseant drug. Elevated relative risks were found for congenital hip deformity (relative risk estimate of 1.4, with 95 percent confidence limits of 1.1 to 1.8), congenital hip dislocation (relative risk estimate of 1.7, with 95 percent confidence limits of 1.2 to 2.4), female genital anomalies (relative risk of 16.4, with 95 percent confidence limits of 3.5 to 78), intestinal fixation anomalies (relative risk of 3.6, with 95 percent confidence limits of 1.2 to 9.9), and iris/ciliary body defects (relative risk estimate of 7.5, with 95 percent confidence limits of 2.3 to 23). The investigator stated that associations should be considered screening signals that require further study and confirmation in other studies. The investigator concluded that this unadjusted profile of 457 suspected birth defect outcomes with 5,995 first

trimester exposures to the anti-nauseant drug containing doxylamine generally supports lack of teratogenicity for the birth defects studied. He added that further study of female genital organ anomalies (relative risk estimate of 16.4) is desirable because nausea in pregnancy relates to maternal sex hormone levels.

The agency has reviewed extensive data concerning the possible teratogenicity of doxylamine succinate and concludes that it is unlikely that this ingredient is a teratogen. The agency recognizes that even the large number of pregnancies evaluated in the numerous studies discussed above cannot rule out the possibility that doxylamine succinate has a weak teratogenic potential. However, the agency believes that this ingredient can be safely marketed OTC as an antihistamine when labeled with the pregnancy/nursing warning required in 21 CFR 201.63. (See comment 2 below.) Therefore, doxylamine succinate is being included in the tentative final monograph.

References

- (1) Eskenazi, B., and M.B. Bracken, "Bendectin (Debendox) As a Risk Factor for Pyloric Stenosis," *American Journal of Obstetrics and Gynecology*, 144:919-924, 1982.
- (2) Aselton, P.J., et al., "Pyloric Stenosis and Maternal Bendectin Exposure," *American Journal of Epidemiology*, 120:251-256, 1984.
- (3) Aselton, P.J., et al., "First-Trimester Drug Use and Congenital Disorders," *American Journal of Obstetrics and Gynecology*, 65:451-455, 1985.
- (4) Mitchell, A.A., et al., "Birth Defects in Relation to Bendectin Use in Pregnancy, II. Pyloric Stenosis," *American Journal of Obstetrics and Gynecology*, 147(7):737-742, 1983.
- (5) Rosa, F.W., draft of unpublished study, OTC Volume 04HTFM, Docket No. 76N-052H, Dockets Management Branch.
- (6) Fleming, D.M., J.D.E. Knox, and D.L. Crombie, "Debendox in Early Pregnancy and Fetal Malformations," *British Medical Journal*, 283:99-101, 1981.
- (7) Michaelis, J., et al., "Prospective Study of Suspected Associations Between Certain Drugs Administered During Early Pregnancy and Congenital Malformations," *Teratology*, 27:57-64, 1983.
- (8) Milkovich, L., and B.J. Van Den Berg, "An Evaluation of the Teratogenicity of Certain Anti-nauseant Drugs," *American Journal of Obstetrics and Gynecology*, 125(2):244-248, 1976.

(9) Hendrickx, A.G., et al., "Evaluation of Bendectin Embryotoxicity in Nonhuman Primates: I. Ventricular Septal Defects in Prenatal Macaques and Baboons," *Teratology*, 32:179-189, 1985.

(10) Hendrickx, A.G., et al., "Evaluation of Bendectin Embryotoxicity in Nonhuman Primates. II. Double Blind Study in Term Cynomolgus Monkeys," *Teratology*, 32:191-194, 1985.

(11) Kalter, H., and J. Warkany, "Congenital Malformations: Etiologic Factors and Their Role in Prevention (First of Two Parts)," *New England Journal of Medicine*, 308:424-431, 1983.

(12) Holmes, L.B., "Teratogen Update: Bendectin," *Teratology*, 27:277-281, 1983.

(13) MacMahon, B., "Editorial. More on Bendectin," *Journal of the American Medical Association*, 246(4):371-372, 1981.

(14) Brent, R.R., "Editorial. The Bendectin Saga: Another American Tragedy (Brent, '80)," *Teratology*, 27:283-286, 1983.

(15) Leeder, J.S., S.P. Spielberg, and S.M. MacLeod, "Editorial. Bendectin: The Wrong Way to Regulate Drug Availability," *Canadian Medical Association Journal*, 129:1085-1087, 1983.

(16) Mitchell, A.A., et al., "Birth Defects Related to Bendectin Use in Pregnancy, I. Oral Clefts and Cardiac Defects," *Journal of the American Medical Association*, 245(22):2311-2314, 1981.

(17) Golding, J., S. Vivian, and J.A. Baldwin, "Maternal Anti-nauseants and Clefts of Lip and Palate," *Human Toxicology*, 2:63-73, 1983.

(18) Rothman, K.J., et al., "Exogenous Hormones and Other Drug Exposures of Children with Congenital Heart Disease," *American Journal of Epidemiology*, 109(4):433-439, 1979.

(19) Correy, J.F., and N.M. Newman, "Debendox and Limb Reduction Deformities," *Medical Journal of Australia*, 1:417-418, 1981.

(20) Aselton, P.J., et al., "Additional Follow-up of Congenital Limb Disorders in Relation to Bendectin Use," *Journal of the American Medical Association*, 250(1):33-34, 1983.

(21) Jiok, H., et al., "First-Trimester Drug Use and Congenital Disorders," *Journal of the American Medical Association*, 246:343-346, 1981.

(22) McCredie, J., et al., "The Innocent Bystander," *The Medical Journal of Australia*, 140:525-527, 1984.

(23) David, T.J., "Debendox Does Not Cause the Poland Anomaly," *Archives of Disease in Children*, 57:479-480, 1982.

(24) Hearey, C.D., et al., "Investigation of a Cluster of Anencephaly and Spina

- Bifida," *America Journal of Epidemiology*, 120:559-564, 1984.
- (25) Robinson, H.B., and K. Tross, "Agenesis of the cloacal membrane—A Probable Teratogenic Anomaly," *Perspectives in Pediatric Pathology*, 1(1):79-96, 1984.
- (26) Cordero, J.F., et al., "Is Bendectin a Teratogen?" *Journal of the American Medical Association*, 245(22):2307-2310, 1981.
- (27) Cordero, J.F., and G.P. Oakley, "Drug Exposure During Pregnancy: Some Epidemiologic Considerations," *Clinical Obstetrics and Gynecology*, 26(2):418-428, 1983.
- (28) Smithells, R.W., and S. Sheppard, "Teratogenicity Testing in Humans: A Method Demonstrating Safety of Bendectin," *Teratology*, 17:31-36, 1978.
- (29) Heinonen, O.P., D. Slone, and S. Shapiro, "Antinauseants, and Phenothiazines" in *Birth Defects and Drugs in Pregnancy*, PSG Publishing, Littleton, MA, pp. 322-334, 1977.
- (30) Newman, N.M., J.F. Correy, and G.I. Dudgeon, "A Survey of Congenital Abnormalities and Drugs in a Private Practice," *Australian and New Zealand Journal of Obstetrics and Gynecology*, 17:156-159, 1977.
- (31) Michaels, J., et al., "Teratogene Effekte von Lenotan?", *Deutsches Arzteblatt*, 23:1527-1529, 1980.
- (32) Bunde, C.A., and D.M. Bowles, "A Technique for Controlled Survey of Case Records," *Current Therapeutic Research*, 5:245-248, 1963.
- (33) Aselton, P., et al., "First-Trimester Drug Use and Congenital Disorders," *Obstetrics and Gynecology*, 65(4):451-455, 1985.
- (34) Morelock, et al., "Bendectin and Fetal Development—A Study at Boston City Hospital," *American Journal of Obstetrics and Gynecology*, 142(2):209-213, 1962.
- (35) Harron, D.W.G., K. Griffiths, and R.C. Shanks, "Debendox and Congenital Malformations in Northern Ireland," *British Medical Journal*, 281:1379-1381, 1980.
- (36) Shapiro, S., et al., "Antenatal Exposure to Doxylamine Succinate and Dicyclomine Hydrochloride (Bendectin) in Relation to Congenital Malformations, Perinatal Mortality Rate, Birth Weight, and Intelligence Quotient Score," *American Journal of Obstetrics and Gynecology*, 128(5):480-485, 1977.
- (37) Gibson, G.T., et al., "Congenital Anomalies in Relation to the Use of Doxylamine/Dicyclomine and Other Antenatal Factors," *The Medical Journal of Australia*, 1:410-414, 1981.
- (38) Greenberg, G., et al., "Maternal Drug Histories and Congenital Abnormalities," *British Medical Journal*, 2:853-856, 1977.
- (39) Clarke, M., and D.B. Clayton, "Safety of Debendox (Bendectin)," *Lancet*, 1:659-660, 1981.
- (40) Memorandum of telephone conversation between A.J. Mustafa, FDA, and J.F. Cordero, Center for Disease Control, dated July 15, 1986, in OTC Volume 04ATFM, Docket No. 76N-052H, Dockets Management Branch.
- (41) Rosa, F.W., "Computerized On-Line Medicaid Pharmaceutical Surveillance System (COMPASS) Human Teratology," presentation at the Teratology Society Meeting, July 8, 1986, Boston, MA, in OTC Volume 04ATFM, Docket No. 76N-052H, Dockets Management Branch.
2. Two comments urged that doxylamine succinate not be made available as an OTC antihistamine drug product. These comments stated that doxylamine succinate is used primarily in a prescription drug product that is marketed as an antinauseant to be taken during pregnancy. The comments expressed the concern that pregnant women might take OTC antihistamine drug products containing doxylamine succinate to self-medicate for nausea during the critical first trimester of pregnancy.
- A reply comment advocated OTC status for doxylamine succinate because it has been sold OTC as an antihistamine at a dosage of 7.5 milligrams (mg) since the 1950's. The comment stated that doxylamine succinate in OTC drug products is labeled for use as an antihistamine, not as an antinauseant for use during pregnancy. The comment added that there did not seem to be any information suggesting that pregnant women had used antihistamine drug products containing doxylamine succinate as an antinauseant during the long period of time that they have been marketed OTC. The comment also stated that the prescription drug product containing doxylamine succinate that is used as an antinauseant during pregnancy has been shown to be safe by many studies. The comment cited six of these studies (Refs. 1 through 6). (Note: In June 1983, the marketing of the above mentioned prescription drug product was discontinued voluntarily by the manufacturer.)
- The agency agrees with the reply comment. Doxylamine succinate can be generally recognized as safe and effective as an antihistamine in OTC drug products for the temporary relief of symptoms of allergic rhinitis and the common cold. (See comment 1 above.) Doxylamine succinate at the 7.5-mg dosage level has been sold as an OTC antihistamine in cough-cold products for many years. The comments that objected to the OTC marketing of this drug did not present any data and the agency is not aware of any data, indicating that pregnant women have used OTC cough-cold drug products containing doxylamine succinate to self-medicate for nausea during pregnancy. The OTC antihistamine drug products will be labeled only for use to relieve symptoms of allergic rhinitis and the common cold.
- In addition, in the *Federal Register* of December 3, 1982 (47 FR 54750), the agency published a final rule requiring the following pregnancy warning in the labeling of all OTC drug products that are intended for systemic absorption into the body: "As with any drug, if you are pregnant or nursing a baby, seek the advice of a health professional before using this product." The agency believes that the proposed labeling for doxylamine succinate in this amendment to the tentative final monograph and the required warning concerning the use of OTC drug products during pregnancy are adequate to prevent misuse during pregnancy and to allow for general recognition of doxylamine succinate as safe and effective for OTC use as an antihistamine.

References

- (1) Bunde, C. A., and D. M. Bowles, "A Technique for Controlled Survey of Case Records," *Current Therapeutic Research*, 5:245-248, 1963.
- (2) Bunde, C. A., and H. M. Leyland, "A Controlled Retrospective Survey in Evaluation of Teratogenicity," *Journal of New Drugs*, 5:193-198, 1965.
- (3) Gibson, J. P., et al., "Teratogenicity and Reproduction Studies with an Antinauseant," *Toxicology and Applied Pharmacology*, 13:439-447, 1968.
- (4) Milkovich, L., and B. J. Van Den Berg, "An Evaluation of the Teratogenicity of Certain Antinauseant Drugs," *American Journal of Obstetrics and Gynecology*, 125:244-248, 1976.
- (5) Warnecke, C., "Die Behandlung des Schwangerschaftserbrechens mit Lenotan," *Medizinische Monatsschrift*, 17:691-694, 1963.
- (6) Yershalmy, J., and L. Milkovich, "Evaluation of the Teratogenicity Effect of Medicine in Man," *American Journal of Obstetrics and Gynecology*, 93:553-562, 1965.
3. Several comments disagreed with the Panel's recommendation to allow the OTC marketing of doxylamine succinate at dosage levels greater than 7.5 mg. Such dosage strengths had previously been available by prescription only. In

general, the comments expressed opinions, without supporting data, that the benefits obtained from allowing higher dosage levels of this ingredient in OTC drug products would not outweigh the risks to which consumers would be exposed. Among the risks mentioned were a pronounced tendency to produce drowsiness and other adverse reactions. The comments also expressed concern that asthmatics with severe bronchitis would suffer from a thickening of secretions due to the anticholinergic effect of antihistamines.

In the preamble to the Panel's report at 41 FR 38313, the agency disagreed with the Panel's Category I classification of doxylamine succinate at dosage levels greater than 7.5 mg, i.e., adult dosages of 7.5 to 12.5 mg every 4 to 6 hours. The agency's objection to the OTC marketing of doxylamine succinate at dosages greater than 7.5 mg was based on the drowsiness that may result when this ingredient is used at higher doses. Subsequently, in a final decision concerning the marketing of diphenhydramine hydrochloride as an OTC antitussive drug product, published in the *Federal Register* of August 31, 1979 (44 FR 51512), the Commissioner found that the risk of drowsiness in itself does not justify restricting a drug to prescription use if "the manufacturer provides essential information in the labeling." Therefore, the dosages for doxylamine succinate recommended by the Panel are being adopted.

The following directions for use are being included in the tentative final monograph: Adults and children 12 years of age and over: oral dosage is 7.5 to 12.5 milligrams every 4 to 6 hours, not to exceed 75 milligrams in 24 hours, or as directed by a doctor. Children 6 to under 12 years of age: oral dosage is 3.75 to 6.25 milligrams every 4 to 6 hours, not to exceed 37.5 milligrams in 24 hours, or as directed by a doctor. Children under 6 years of age: consult a doctor. Also, the following directions for use are being included in proposed § 341.90 *Professional labeling*: Children 2 to under 6 years of age: oral dosage is 1.9 to 3.125 milligrams every 4 to 6 hours, not to exceed 18.75 milligrams in 24 hours.

The warnings proposed in §§ 341.72(c)(1) and (2), which are general warnings for all OTC antihistamine drug products and which include a warning to persons with asthma and chronic pulmonary disease not to take this drug unless directed by a doctor, are also proposed for doxylamine succinate. These warnings are in addition to the warning in proposed § 341.72(c)(4) that concerns drowsiness. The agency is proposing

that this warning be revised to advise consumers that, in addition to alcohol, sedative and tranquilizer drug products intensify the drowsiness effect of antihistamines. The warning is revised to read, "May cause marked drowsiness; alcohol, sedatives, and tranquilizers may increase the drowsiness effect. Avoid alcohol while taking this product. Do not take this product if you are taking sedatives or tranquilizers, without first consulting your doctor. Use caution when driving a motor vehicle or operating machinery."

4. One comment questioned the dosage of doxylamine succinate when used as an antihistamine. The comment stated that, in comparing doxylamine succinate with promethazine, the Panel stated that "Doxylamine has also been described as being slightly 'less potent' than promethazine but having a longer duration of action" (41 FR 38386). However, the Panel recommended a dosage for doxylamine of "every 4 to 6 hours" and for promethazine of "every 8 to 12 hours." The comment concluded that the Panel, in effect, recommended that an ingredient having a longer duration of action be taken more frequently, and requested clarification of this apparent discrepancy.

The agency has reviewed the reference cited in the Panel's report that describes the duration of action for doxylamine and promethazine (Ref. 1). The agency has determined that the reference was misquoted. Promethazine is actually the active ingredient described as having a "longer duration of action" rather than doxylamine as stated in the Panel's report. Therefore, a more frequent dosage schedule for doxylamine is appropriate.

Reference

(1) Modell, W., "Drugs of Choice, 1974-1975," The C.V. Mosby Co., St. Louis, p. 426, 1974.

5. One comment noted an apparent oversight in the Panel's conclusion on the dosage for doxylamine succinate and suggested that the words "for adults" be added to clarify the Panel's conclusion (41 FR 38386). As changed, the statement would read: "The Panel concludes that doxylamine succinate 7.5 mg is the minimum effective OTC dosage for adults for the relief of the symptoms of allergic rhinitis."

The agency agrees with this change. The Panel stated in its dosage discussion of doxylamine succinate and in § 341.12(d) of its recommended monograph that the adult oral dosage of this drug is 7.5 to 12.5 mg every 4 to 6 hours, not to exceed 75 mg in 24 hours.

6. One comment stated that it was unaware of any clinical evidence that

doxylamine succinate causes excitability in children. The comment added that the existing evidence demonstrates that doxylamine succinate does not cause excitability in children 6 years of age and over, citing attachments 17 (Ref. 1) and 18 (Ref. 2) in OTC Volume 040264 to support its contention. The comment recommended that the label warning recommended by the panel in § 341.72(b)(1), which states "May cause excitability especially in children," not be required for doxylamine succinate.

The agency does not agree with the comment's recommendation. The agency has reviewed the references cited above. These articles primarily report the results of studies in children conducted to determine the effectiveness of doxylamine succinate in various conditions. The evaluation of side effects, such as excitability, was not the primary purpose of the studies. The authors, in fact, did not mention whether excitability did or did not occur. The fact that excitability was not discussed or measured in the studies is not a sufficient basis to conclude that excitability does not occur, and that the warning recommended in § 341.72(b)(1) is not needed.

The Panel's report at 41 FR 38380 recognizes that "among the antihistamines, there are minor differences in the nature and frequency of side effects and toxicity which are related to chemical class." The incidence and severity of adverse effects, and the dose that causes these effects, vary with each drug and each individual. It should be noted that antihistamines as a class have both depressant and stimulant effects on the central nervous system (Ref. 3). Central nervous system depression manifested by drowsiness is the most common side effect. However, patients given conventional doses may occasionally become restless, nervous, and unable to sleep (Ref. 4).

In children, antihistamines can have a stimulating effect instead of the usual sedative effect which commonly occurs in adults (Ref. 5). Because antihistamines, as a pharmacologic group, can cause excitability, especially in children, and this effect cannot be predicted for an individual or for a specific antihistamine, the agency concludes that the warning is applicable to all antihistamines. Until data are presented that clearly show that doxylamine succinate or any other Category I antihistamine does not cause excitability in children, the agency believes that the consumer should be warned of this possible side effect.

Therefore, the agency proposes that the warning "May cause excitability especially in children," be required for all antihistamine active ingredients.

References

- (1) Cany, J. and H. Huidobro, "Etude Clinique et Experimentale de l'activite Antihistaminique du Succinate de Doxylamine," *Therapie*, 15:159-167, 1960.
- (2) Lajouanine, P., H. Roure, and A. Maurice, "Etude Clinique du Succinate de Doxylamine en Pediatrie," *Gazette Medicale de France*, 69:2429-2434, 1962.
- (3) "AMA Drug Evaluations," 2d Ed., Publishing Sciences Group, Acton, MA, pp. 491-492, 1973.
- (4) Douglas, W.W., "Histamine and Antihistamine; 5-Hydroxytryptamine and Antagonists," in "The Pharmacological Basis of Therapeutics," 4th Ed., edited by L. S. Goodman and A. Gilman, The Macmillan Co., New York, pp. 635-642, 1970.
- (5) "Evaluation of Drug Interactions," 2d Ed., American Pharmaceutical Association, Washington, pp. 377-380, 1976.

B. Comments on Dosages for Triprolidine Hydrochloride.

7. Two comments requested that the agency's proposed dosage of 2.5 mg every 6 to 8 hours for triprolidine hydrochloride (50 FR 2217) be changed to a dosage of 2.5 mg every 4 to 6 hours, with the 24-hour maximum dose to remain 10 mg. Both comments stated that a dosing frequency of every 6 to 8 hours, as proposed in the tentative final monograph, is inconsistent with the dosing frequency of every 4 to 6 hours that had been approved by the agency, under the new drug approval procedures, for several currently marketed OTC antihistamine drug products at the same adult dosage levels of 2.5 mg triprolidine hydrochloride.

One comment, from a manufacturer that currently markets OTC triprolidine hydrochloride drug products under approved supplemental new drug applications (NDA's), stated that the safety and efficacy data in support of a dosing frequency of 2.5 mg every 4 to 6 hours are contained in its NDA's and, if necessary, could also be submitted to the agency's docket for the OTC antihistamine rulemaking. The other comment contended that the agency's proposed dosing frequency of 2.5 mg every 6 to 8 hours would preclude combining triprolidine hydrochloride as an antihistamine with any nasal decongestant active ingredient. The comment explained that the dosing frequencies proposed by the agency in the nasal decongestant tentative final

monograph (50 FR 2239) of every 4 hours for phenylephrine hydrochloride and every 4 to 6 hours for pseudoephedrine hydrochloride and pseudoephedrine sulfate are inconsistent with the 6 to 8 hour dosing frequency for triprolidine hydrochloride. The comment argued that the preclusion of combination drug products containing triprolidine hydrochloride and a nasal decongestant would contradict the Panel's Category I recommendation for combinations of an antihistamine and a nasal decongestant.

The dosing frequency for triprolidine hydrochloride of 2.5 mg every 6 to 8 hours, initially proposed by the agency in the tentative final monograph, was based on the labeling in approved NDA's for prescription drug products containing this ingredient. This labeling stated that the adult dosage is 2.5 mg "3-4 times a day" (Ref. 1). Three to four times a day was construed to be one dose every 6 to 8 hours over a 24-hour period of time.

The agency has reviewed several published studies cited by one comment in its approved supplemental NDA's and agrees that the studies support a dosing frequency of 2.5 mg every 4 to 6 hours for triprolidine hydrochloride (Refs. 2, 3, and 4). One double-blind study involving 184 adults with a history of ragweed allergy compared the effectiveness of triprolidine hydrochloride alone, pseudoephedrine hydrochloride alone, triprolidine hydrochloride and pseudoephedrine hydrochloride in combination, and a placebo in reducing symptoms of allergic rhinitis (Ref. 2). A symptom complex score comprised of "nose blows, sneezing, rhinorrhea and nasal itch, lacrimation and itching of the eyes, ears and oral cavity" was used to measure the effectiveness of the different medications in treating symptoms of allergic rhinitis. On the first treatment day, 47 test subjects received 2.5 mg triprolidine hydrochloride at 11:30 a.m., 5:30 p.m., and 11:30 p.m. The mean of the square root of the allergic rhinitis symptom complex score for the 47 patients reached a minimum, i.e., the symptoms monitored were reduced to the greatest extent, when measured at 2:30 p.m. (3 hours after the initial dose at 11:30 a.m.). The mean began to increase after 2:30 p.m., indicating an increase in symptoms. Symptom complex scores were not measured after the 5:30 p.m. and 11:30 p.m. doses. On the second day the same 47 test subjects received 2.5 mg triprolidine hydrochloride at 8:30 a.m. and 2:30 p.m. The mean of the square root of the allergic rhinitis symptom complex score for the 47 patients taking triprolidine hydrochloride reached a

minimum at 12:30 p.m. (4 hours after the 8:30 a.m. dose) and began to increase after 12:30 p.m. These data suggest that the effectiveness of triprolidine hydrochloride in treating symptoms of allergic rhinitis begins to decrease 3 to 4 hours after a dose has been taken. In addition, the mean of the square root of the allergic rhinitis symptom complex score for the triprolidine hydrochloride test group at 8:30 a.m. on the second day of the study, 9 hours after the 11:30 p.m. dose taken on the first day, was equivalent to the baseline mean of the square root of the symptom complex score for this group measured at the time the initial dose was given at 11:30 a.m. on the first day of the study. These data suggest that after 9 hours a dose of 2.5 mg triprolidine is no longer effective in reducing symptoms of allergic rhinitis.

A double-blind crossover study involving eight healthy male volunteers aged 21 to 50 years studied the effects of triprolidine hydrochloride and cyclizine hydrochloride in inhibiting the skin response to injected histamine. Subjects were studied on four occasions at weekly intervals. Each of the eight subjects received all of the following four treatments, one treatment each week: lactose placebo, 2.5 mg triprolidine hydrochloride, 50 mg cyclizine hydrochloride, and 100 mg cyclizine hydrochloride (Ref. 3). Inhibition of flare and weal responses to intradermal injections of histamine were assessed following these dosages of triprolidine hydrochloride, cyclizine hydrochloride, or lactose. At 1, 2, and 4 hours after the dose was given, three intradermal injections of histamine (0.1, 0.4, and 1.6 micrograms) were made into the back of the test subjects. Twenty minutes after injecting the histamine each flare and weal was measured. Significant displacement of dose-response curves, indicating the inhibition of a skin response to histamine, occurred at 1, 2, and 4 hours after 2.5 mg doses of triprolidine hydrochloride. However, the magnitude of the displacement of the dose-response curves decreased from 5.95 at 2 hours to 3.96 at 4 hours indicating that the effectiveness of 2.5 mg triprolidine hydrochloride to inhibit a skin response to histamine began to decrease between 2 and 4 hours after the drug had been given.

A double-blind crossover placebo-controlled bioavailability study in 18 healthy volunteers examined blood plasma levels of triprolidine hydrochloride in subjects taking a combination drug containing triprolidine hydrochloride and pseudoephedrine hydrochloride in an immediate release

dosage form. The study compared this group to subjects taking the same combination drug in a sustained release dosage form (Ref. 4). The test drugs included (1) sustained release capsules containing 5 mg triprolidine hydrochloride and 120 mg pseudoephedrine hydrochloride, (2) immediate release tablets containing 2.5 mg triprolidine hydrochloride and 60 mg pseudoephedrine hydrochloride, and (3) placebo tablets and capsules. The volunteers took the test drugs over a 5-day period. Sustained release capsules containing the combination of active drugs were given alternately with placebo capsules each day according to the following dosage in order to parallel the immediate release dosage schedule: an active drug combination capsule at 8 a.m., a placebo capsule at 2 p.m., an active drug combination capsule at 8 p.m., and a placebo capsule at 2 p.m. Immediate release capsules containing the combination of active drugs were given each day according to the following schedule: one tablet every 6 hours at 8 a.m., 2 p.m., 8 p.m., and 2 a.m. On the fifth day, blood samples were drawn at 8 a.m., 9 a.m., 10 a.m., 12 p.m., 2 p.m., 3 p.m., 4 p.m., 6 p.m., 8 p.m., and 10 p.m. These samples were measured to determine steady-state blood plasma levels for triprolidine hydrochloride and pseudoephedrine hydrochloride following the administration of the sustained release dosage form and following the administration of the immediate release dosage form. The mean triprolidine plasma levels measured for the immediate release dosage form on the fifth day reached an averaged maximum level at 1.6 hours with a range of 1 to 4 hours after the 8 a.m. and 2 p.m. doses. Six hours after each of these immediate release doses, the triprolidine hydrochloride plasma levels decreased to approximately 55 percent of the maximum levels measured. In addition, DeAngelis, et al. (Ref. 5) found a half-life of 5 hours for triprolidine hydrochloride.

Based on a review of the above published studies and on currently approved labeling of OTC drug products containing triprolidine hydrochloride (Ref. 6), the agency concludes that a dosing frequency of every 4 to 6 hours for both adults and children is appropriate for triprolidine hydrochloride and has revised the proposed directions for OTC use (§ 341.72(d)(10), redesignated as § 341.72(d)(12)) and the proposed directions for professional use of this drug (§ 341.90(k), redesignated § 341.90(m)), to read as follows:

(12) For products containing triprolidine hydrochloride identified in § 341.12(1). Adults and children 12 years of age and over: oral dosage is 2.5 milligrams every 4 to 6 hours, not to exceed 10 milligrams in 24 hours, or as directed by a doctor. Children 6 to under 12 years of age: oral dosage is 1.25 milligrams every 4 to 6 hours, not to exceed 5 milligrams in 24 hours, or as directed by a doctor. Children under 6 years of age: consult a doctor.

(m) For products containing triprolidine hydrochloride identified in § 341.12(1). Children 4 to under 6 years of age: oral dosage is 0.938 milligram every 4 to 6 hours, not to exceed 3.744 milligrams in 24 hours. Children 2 to under 4 years of age: oral dosage is 0.625 milligram every 4 to 6 hours, not to exceed 2.5 milligrams in 24 hours. Infants 4 months to under 2 years of age: oral dosage is 0.313 milligram every 4 to 6 hours, not to exceed 1.252 milligrams in 24 hours.

References

- (1) Copies of FDA-approved labeling from NDA 11-110 and NDA 11-496, OTC Volume 04HTFM, Docket No. 76N-052H, Dockets Management Branch.
- (2) Connell, J.T., et al., "A Double-Blind Controlled Evaluation of Actifed and its Individual Constituents in Allergic Rhinitis," *Journal of International Medical Research*, 10:341-347, 1982.
- (3) Hamilton, M., et al., "A Comparison of Triprolidine and Cyclizine on Histamine (H₁) Antagonism, Subjective Effects and Performance Tests in Man," *British Journal of Clinical Pharmacology*, 13:441-444, 1982.
- (4) Perkins, J.G., et al., "A Bioavailability and Safety Study Comparing Actifed Sustained-Action (SA) Capsules to Actifed Immediate-Release (IR) Tablets," *Current Therapeutic Research*, 28(5):650-668, 1980.
- (5) DeAngelis, R.L., M.F. Kearney, and R.M. Welch, "Determination of Triprolidine in Human Plasma by Quantitative TLC," *Journal of Pharmaceutical Science*, 66:841-843, 1977.
- (6) Copies of FDA-approved labeling from NDA 11-110 and NDA 11-496, OTC Volume 04HFM, Docket No. 76N-052H, Dockets Management Branch.

II. The Agency's Proposals Concerning Chlorcyclizine Hydrochloride

Chlorcyclizine hydrochloride, as a single ingredient antihistamine at a 50-mg oral dose, was first marketed under an approved NDA in 1949 (Ref. 1). It was approved for OTC marketing at a 25-mg dose in 1959 and at this dose has been exempted from the prescription dispensing requirements of section 503(b)(1)(C) of the Federal Food, Drug,

and Cosmetic Act (21 U.S.C. 353(b)(1)(c)) since August 21, 1959 (24 FR 6805). (See 21 CFR 310.201(a)(25).) Chlorcyclizine hydrochloride (25 mg) in combination with pseudoephedrine hydrochloride (30 mg) at a dosage of one tablet three times a day has been marketed OTC under an approved NDA since 1959 (Ref. 2).

Drug products containing chlorcyclizine hydrochloride as a single ingredient and in combination with pseudoephedrine were reviewed under the agency's Drug Efficacy Study Implementation (DESI) Program. In DESI notices published in the *Federal Register* of July 27, 1972 (37 FR 15030) and July 29, 1976 (41 FR 31592), FDA stated its conclusion that chlorcyclizine hydrochloride (25 and 50 mg) is effective for relieving seasonal and perennial allergic rhinitis and vasomotor rhinitis. The latter notice noted that the manufacturer had discontinued marketing the 50-mg product in 1968. In a July 8, 1972 DESI notice (37 FR 13494), the Panel on Drugs Used in Allergy of the DESI Group stated that chlorcyclizine hydrochloride (25 mg) in combination with pseudoephedrine hydrochloride (30 mg) was effective in relieving hay fever, but was ineffective as a fixed combination in relieving nasal congestion because the dose of pseudoephedrine was less than optimal. The July 8, 1972 notice, which pertained to the review of OTC drugs by the DESI group, also deferred implementation of the Drug Efficacy Study pending the results of the OTC drug review. The OTC dose of pseudoephedrine was discussed in the advance notice of proposed rulemaking for OTC cold, cough, allergy, bronchodilator, and antiasthmatic drug products (September 9, 1976; 41 FR 38402) and in the tentative final monograph for OTC nasal decongestant drug products (January 15, 1985; 50 FR 2229).

No data on chlorcyclizine hydrochloride were submitted to the Cough-Cold Panel, and the ingredient was not reviewed as part of the OTC drug review. At this time, chlorcyclizine hydrochloride is being included in this amendment to resolve administrative questions that may have arisen concerning its status.

A review of FDA adverse reaction reports since 1969 indicates that only one adverse reaction, i.e., a report of "no drug effect," has been reported for a chlorcyclizine hydrochloride-containing drug product (Ref. 3). Based on the DESI reviews mentioned above that support the effectiveness of the drug as an antihistamine, and the long history of safe marketing as an OTC antihistamine, the agency concludes that

chlorcyclizine hydrochloride (25 mg) can be generally recognized as safe and effective for OTC use. The agency therefore is proposing Category I for this ingredient.

The labeling requirements for OTC antihistamine drug products in § 341.72 are also applicable to drug products containing chlorcyclizine hydrochloride. Based on the NDA labeling for chlorcyclizine hydrochloride products, the dosage recommended in § 310.201(a)(25), and other data (Ref. 4), the agency proposes the following dosage for chlorcyclizine hydrochloride: Adults and children 12 years of age and over: 25 milligrams every 6 to 8 hours, not to exceed 75 milligrams in 24 hours, or as directed by a doctor. Children under 12 years of age: Consult a doctor. Additionally, based on the pediatric dosage recommendations in § 310.201(a)(25)(vi), and the general guidelines used by the Cough-Cold Panel for determining pediatric dosages (41 FR 38333), the following dosages for chlorcyclizine hydrochloride for pediatric use are included in professional labeling in § 341.90: *For products containing chlorcyclizine hydrochloride identified in § 341.12(b).* Children 6 to under 12 years of age: Oral dosage is 12.5 milligrams every 6 to 8 hours, not to exceed 37.5 milligrams in 24 hours. Children 2 to under 6 years of age: Oral dosage is 6.25 milligrams every 6 to 8 hours, not to exceed 18.75 milligrams in 24 hours.

In 1966, acting on the recommendation of an Ad Hoc Advisory Committee on the Teratogenic Effect of Certain Drugs, FDA required relabeling, through NDA supplements, of drug products containing chlorcyclizine hydrochloride, cyclizine hydrochloride, and meclizine hydrochloride to include the following specific warning: "Warning—Not for use by women who are pregnant or who may possibly become pregnant, unless directed by a physician, since this drug may have the potentiality of injuring the unborn child." This labeling warning was prompted by concern that the drugs may have teratogenic or embryolethal potential. This required labeling statement (and others which are covered by this rulemaking) is included in 21 CFR 201.307, 310.201(a)(25), 369.20, and 369.21. [Chlorcyclizine hydrochloride, cyclizine hydrochloride, and meclizine hydrochloride are members of the piperazine class of antihistamines. Cyclizine hydrochloride and meclizine hydrochloride are primarily used as antiemetics, i.e., for the prevention and treatment of nausea and vomiting associated with motion sickness.]

Subsequently, in the *Federal Register* of March 13, 1975 (40 FR 12935), the Advisory Review Panel on OTC Laxative, Antidiarrheal, Emetic, and Antiemetic Drug Products concluded that the available data do not warrant a restriction in the use of meclizine hydrochloride or cyclizine hydrochloride or the need for a pregnancy warning (40 FR 12935). The Panel based its conclusion on a review of the report of the FDA Ad Hoc Advisory Committee in light of more recent epidemiological data, taking into consideration the position of the American Teratology Society regarding the limitations of extrapolating animal data to man (Ref. 5). Epidemiological data on 50,282 pregnant women, 1,014 of whom had used meclizine hydrochloride during the early stages of pregnancy, indicate that the incidence of malformation of the offspring of the 1,014 women was not statistically greater than that of the control group (who had taken other drugs during pregnancy). Further, there is indirect evidence that meclizine hydrochloride is not toxic to the embryo and that the incidence of specific teratogenicity, e.g., cleft palate, was lower in the human pregnancy data than might have been expected from the results of the animal teratogenicity studies that led to the pregnancy warning (Ref. 6). The Panel concluded that the data do not support a restriction in the use of meclizine hydrochloride or cyclizine hydrochloride or a pregnancy warning. FDA agreed with the Panel on this issue in the tentative final monograph for OTC antiemetic drug products (44 FR 41068). The agency also believes that the data concerning teratology associated with meclizine hydrochloride and cyclizine hydrochloride are equally applicable to chlorcyclizine hydrochloride.

The agency also has reexamined its policy with respect to pregnancy warnings on OTC drugs. On December 5, 1983, the following general pregnancy-nursing warning for all OTC drug products intended for systemic absorption became effective (21 CFR 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." The agency has also evaluated additional human epidemiological data (Ref. 7) and has determined that chlorcyclizine hydrochloride, as well as cyclizine hydrochloride and meclizine hydrochloride, has not been established to be a human teratogen. The agency concludes that the general pregnancy warning required by § 201.63 is sufficient for OTC drug products

containing these ingredients. The prescription drug labeling pregnancy precautions required by § 201.57(f)(6) are sufficient for prescription drug products containing these ingredients. Therefore, the specific pregnancy warning that has been required for chlorcyclizine, cyclizine, and meclizine or their salts in § 201.307 should be removed. In the final rule for OTC antiemetic drug products (April 30, 1987; 52 FR 15886), the agency stated that because the requirements of § 201.307 with respect to cyclizine hydrochloride and meclizine hydrochloride are superseded by the requirements of the antiemetic final rule, the agency would address removal of § 201.307 in a future *Federal Register* publication. In this document, the agency is proposing to remove §§ 201.307 and 310.201(a)(25)(vii)(c) as well as the warnings in § 369.20 and § 369.21 that pertain to the specific pregnancy warning for chlorcyclizine. This action will result in the complete removal of § 201.307 from the CFR.

In addition, the agency is proposing to remove all other portions of § 310.201(a)(25), because the provisions of that regulation will be superseded by the requirements of the final monograph for OTC antihistamine drug products (Part 341). For this same reason, those portions of § 369.20 and § 369.21 applicable to chlorcyclizine are also proposed to be removed.

Chlorcyclizine hydrochloride was not considered by an OTC advisory review panel and, therefore, does not meet the terms of the enforcement policy in § 330.13. However, NDA's that allow the OTC marketing of products containing chlorcyclizine hydrochloride have been approved by the FDA, and the drug has been marketed OTC for many years. Thus, FDA does not believe it is necessary to prohibit OTC marketing of chlorcyclizine hydrochloride under this proposal while public comments to its proposed monograph status are being evaluated. OTC marketing may be initiated subject to the terms and conditions specified in this amendment and in § 341.72 of the tentative final monograph for OTC antihistamine drug products (50 FR 2216) and subject to the risk that FDA may adopt a different position in the final monograph that may require relabeling, recall, or other regulatory action.

References

- (1) Letter from E.E. Nelson, FDA, to Burroughs Wellcome and Co., Inc., OTC Volume 04HATFM, Docket No. 76N-052H, Dockets Management Branch.

(2) Letter from F.J. Talbot, FDA, to Burroughs Wellcome and Co., OTC Volume 04HATFM, Docket No. 76N-052H, Dockets Management Branch.

(3) Department of Health and Human Services, Food and Drug Administration, Adverse Reaction Summary Listings, pertinent pages for the years 1969-1986, OTC Volume 04HATFM, Docket No. 76N-052H, Dockets Management Branch.

(4) Brown, E.A., et al., "A Clinical Evaluation of Chlorcyclizine (Perazil)," *Annals of Allergy*, 8:32-43, 1950.

(5) Staples, R. E., "Teratogens and the Delaney Clause," *Science* 7:185:813-814, 1974.

(6) Shapiro, S., Boston Children's Medical Center, Testimony Before OTC Laxative, Antidiarrheal, Emetic, and Antiemetic Panel, October 11, 1974, in OTC Volume 090PAZ, Dockets Management Branch.

(7) Rosa, F., "Benzhydrylpiperazine (Cyclizines) Terato-Epidemiology," unpublished draft, June 25, 1985, in OTC Volume 04HATFM, Docket No. 76N-052H, Dockets Management Branch.

III. The Agency's Tentative Adoption of the Panel's Recommendations and the Agency's Amendments to the Tentative Final Monograph

A. Summary of Ingredient Categories

The agency has reviewed the active ingredient doxylamine succinate that was submitted to the Panel, as well as other data and information available at this time, and agrees with the Panel's recommendation that this ingredient be Category I. In addition, the agency is proposing that the active ingredient chlorcyclizine hydrochloride, which was not reviewed by the Panel, be Category I. Also, the agency is proposing a revised dosage schedule for the active ingredient triprolidine hydrochloride, which was previously proposed as Category I.

B. Summary of the Agency's Changes in the Tentative Final Monograph

1. Although not reviewed by the Cough-Cold Panel, the agency is proposing that chlorcyclizine hydrochloride be included in this tentative final monograph based on its exemption from the prescription dispensing requirements of the act since 1959 and on previous DESI findings that the drug is effective as an antihistamine. (See Part II. above—the agency's proposals concerning chlorcyclizine hydrochloride.)

2. The agency is proposing that doxylamine succinate be generally recognized as safe and effective at OTC oral dosages for adults and children 12

years of age and over of 7.5 to 12.5 mg every 4 to 6 hours, for children 6 to under 12 years of age of 3.75 to 6.25 mg every 4 to 6 hours, and professional labeling dosages for children 2 to under 6 years of age of 1.9 to 3.125 mg every 4 to 6 hours. (See comments 1 and 3 above.)

3. The agency has revised the letter designations in § 341.12 *Antihistamine active ingredients* to include the addition of the ingredients chlorcyclizine hydrochloride and doxylamine succinate in this section. The agency has revised the letter designations of active ingredients identified in §§ 341.72 (c) and (d) and 341.90 to reflect the revisions in § 341.12. The agency has also revised the number designations of the paragraphs in § 341.72(d) and the letter designations of the paragraphs in § 341.90 to reflect the addition of directions in § 341.72(d) and of professional labeling in § 341.90 for the ingredients chlorcyclizine hydrochloride and doxylamine succinate.

4. The agency is proposing to revise the warnings concerning the drowsiness effect of antihistamine drug products to also include sedatives and tranquilizers as other drugs that may intensify the drowsiness effect of antihistamines. In addition to alcohol, sedative and tranquilizer drugs are known to have additive effects to the drowsiness effect of antihistamine drug products (Refs. 1 and 2). The proposed warning for adults concerning drowsiness is revised to read as follows: "May cause (marked) drowsiness; alcohol, sedatives, and tranquilizers may increase the drowsiness effect. Avoid alcoholic beverages while taking this product. Do not take this product if you are taking sedatives or tranquilizers, without first consulting your doctor. Use caution when driving a motor vehicle or operating machinery." Because children may take prescription drug products that contain sedatives or tranquilizers, the agency is also proposing to revise the warning concerning drowsiness that is required for products labeled for pediatric use only to read as follows: "May cause (marked) drowsiness. Sedatives and tranquilizers may increase the drowsiness effect. Do not give this product to children who are taking sedatives or tranquilizers, without first consulting the child's doctor."

References

(1) Douglas, W. W., "Histamine and 5-Hydroxytryptamine (Serotonin) and Their Agonists," in "The Pharmacological Basis of Therapeutics," 7th Ed., edited by A. G. Gilman et al.,

MaeMillan Publishing Co., New York, p. 621, 1985.

(2) "Histamine and Antihistamines," in "Remington's Pharmaceutical Sciences," 17th Ed., edited by A. R. Gennero, Mack Publishing Co., Easton, PA, pp. 1125-1126, 1985.

5. The agency has revised the proposed directions in § 341.72(d) for all antihistamine active ingredients to read "Adults and children 12 years of age and over: . . ." rather than "Adults: . . ." to provide more informative labeling for the consumer.

6. The agency has revised the proposed directions for OTC use (§ 341.72(d)(10), redesignated as § 341.72(d)(12)) and professional use (§ 341.90(k), redesignated as § 341.90(m)) of triprolidine hydrochloride to include a dosage schedule of every 4 to 6 hours, based on a review of published literature and on current FDA-approved labeling of OTC drug products containing triprolidine hydrochloride under supplemental NDA's. (See comment 7 above.)

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 antihistamine 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 antihistamine 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 substantial or significant economic impact that this amendment would have on OTC antihistamine drug

products. Types of impact may include, but are not limited to, costs associated with relabeling, repackaging, or reformulating. Comments regarding the impact of this amendment on OTC antihistamine 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 matters discussed in this amendment regarding OTC antihistamine drug products, a period of 120 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 amendment in the preamble to the final rule.

The agency has carefully considered the potential environmental effects of this action and has concluded that the action will not have a significant impact on the human environment and that an environmental impact statement is not required. The agency's finding of no significant impact, and the evidence supporting that finding, contained in an environmental assessment, may be seen in the Dockets Management Branch, Food and Drug Administration (address above) between 9 a.m. and 4 p.m., Monday through Friday. This action was considered under FDA's final rule implementing the National Environmental Policy Act (21 CFR Part 25).

The agency is proposing to remove § 201.307 *Chlorcyclizine, cyclizine, meclizine; warnings; labeling requirements* in its entirety, § 310.201(a)(25), and portions of § 369.20 (under the heading "ANTIHISTAMINICS, ORAL") and § 369.21 (under the heading "ANTIHISTAMINICS, ORAL (PHENYLTOLOXAMINE DIHYDROGEN CITRATE, MECLIZINE HYDROCHLORIDE, DOXYLAMINE SUCCINATE, CHLOROTHEN CITRATE, CYCLIZINE HYDROCHLORIDE, AND CHLORCYCLIZINE HYDROCHLORIDE PREPARATIONS")) because the requirements of § 201.307 with respect to cyclizine hydrochloride and meclizine hydrochloride are superseded by the antiemetic final rule (21 CFR Part 336), published in the **Federal Register** of April 30, 1987 (52 FR 15886), and the requirements of § 201.307, § 310.201(a)(25), and the portions of § 369.20 and § 369.21 specified above with respect to chlorcyclizine hydrochloride and/or doxylamine

succinate will be superseded by the antihistamine final monograph (21 CFR Part 341). The portions of §§ 201.307 and 310.201(a)(25) as well as the portions of §§ 369.20 and 369.21 specified above that will be removed and that pertain to the specific pregnancy warning for meclizine, cyclizine, and/or chlorcyclizine preparations are no longer needed because the OTC drug general pregnancy warning required by 21 CFR 201.63 and the prescription drug labeling pregnancy precautions required by 21 CFR 201.57(f)(6) are applicable to these ingredients.

Interested persons may, on or before October 23, 1987, 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 December 22, 1987. 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 August 24, 1988, 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 October 25, 1988. 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 October 25, 1988. 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 201

Labeling, Drugs.

21 CFR Part 310

Administrative practice and procedure, Drugs, Reporting and recordkeeping requirements.

21 CFR Part 341

Labeling, Over-the-counter drugs, Antihistamine drug products.

21 CFR Part 369

Labeling, Medical devices, Over-the-counter drugs.

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 201—LABELING

1. The authority citation for 21 CFR Part 201 is revised to read as follows:

Authority: Secs. 201, 502, 505, 701, 52 Stat. 1040-1042 as amended, 1050-1056 as amended, 21 U.S.C. 321, 352, 355, 371; 21 CFR 5.10 and 5.11.

§ 201.307 [Removed]

2. In Subpart G, Part 201 is amended by removing § 201.307 *Chlorcyclizine, cyclizine, meclizine; warnings; labeling requirements*.

PART 310—NEW DRUGS

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

Authority: Secs. 502, 503, 505, 701, 52 Stat. 1051, 1052, 1053, 1055 as amended (21 U.S.C. 352, 353, 355, 371); 5 U.S.C. 553; 21 CFR 5.10 and 5.11.

§ 310.201 [Amended]

4. In Subpart C, § 310.201 *Exemption for certain drugs limited by new-drug applications to prescription sale* is amended by removing paragraph (a)(25) and reserving it.

PART 341—COLD, COUGH, ALLERGY, BRONCHODILATOR, AND ANTI-ASTHMATIC DRUG PRODUCTS FOR OVER-THE-COUNTER HUMAN USE

5. The authority citation for 21 CFR Part 341 (established in the *Federal Register* of October 2, 1986; 51 FR 35326) is revised to read as follows:

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.

6. In Subpart B, § 341.12 (proposed in the *Federal Register* of January 15, 1985; 50 FR 2200) is revised to read as follows:

§ 341.12 Antihistamine active ingredients.

The active ingredients of the product consist of any of the following when used within the dosage limits established for each ingredient:

- (a) Brompheniramine maleate.
- (b) Chlorcyclizine hydrochloride.
- (c) Chlorpheniramine maleate.
- (d) Dexbrompheniramine maleate.
- (e) Dexchlorpheniramine maleate.
- (f) Diphenhydramine hydrochloride.
- (g) Doxylamine succinate.
- (h) Phenindamine tartrate.
- (i) Pheniramine maleate.
- (j) Pyrilamine maleate.
- (k) Thonzylamine hydrochloride.
- (l) Triprolidine hydrochloride.

7. In Subpart C, § 341.72 (proposed in the *Federal Register* of January 15, 1985; 50 FR 2200) is amended by revising paragraphs (c) (3), (4), (5), (6), and (d)(1); by redesignating paragraphs (d) (2), (3), (4), (5), (6), (7), (8), (9), and (10) as paragraphs (d) (3), (4), (5), (6), (8), (9), (10), (11), and (12), respectively, and revising them; and by adding new paragraphs (d) (2) and (7), and (e) to read as follows:

§ 341.72 Labeling of antihistamine drug products.

* * * * *

(c) * * * * *

(3) For products containing brompheniramine maleate, chlorcyclizine hydrochloride, chlorpheniramine maleate, dexbrompheniramine maleate, dexchlor-pheniramine maleate, phenindamine tartrate, pheniramine maleate, pyrilamine maleate, thonzylamine hydrochloride, or triprolidine hydrochloride identified in § 341.12 (a), (b), (c), (d), (e), (h), (i), (j), (k), and (l). "May cause drowsiness; alcohol, sedatives, and tranquilizers may increase the drowsiness effect. Avoid alcoholic beverages while taking this product. Do not take this product if

you are taking sedatives or tranquilizers, without first consulting your doctor. Use caution when driving a motor vehicle or operating machinery."

(4) For products containing diphenhydramine hydrochloride or doxylamine succinate identified in § 341.12 (f) and (g). "May cause marked drowsiness; alcohol, sedatives, and tranquilizers may increase the drowsiness effect. Avoid alcoholic beverages while taking this product. Do not take this product if you are taking sedatives or tranquilizers, without first consulting your doctor. Use caution when driving a motor vehicle or operating machinery."

(5) For products containing phenindamine tartrate identified in § 341.12 (h). "May cause nervousness and insomnia in some individuals."

(6) For products that are labeled only for use by children under 12 years of age. The labeling of the product contains only the warnings identified in paragraphs (c) (1) and (5) of this section as well as the following:

(i) "Do not give this product to children who have asthma or glaucoma unless directed by a doctor."

(ii) For products containing brompheniramine maleate, chlorpheniramine maleate, dexbrompheniramine maleate, dexchlorpheniramine maleate, phenindamine tartrate, pheniramine maleate, pyrilamine maleate, thonzylamine hydrochloride, or triprolidine hydrochloride identified in § 341.12 (a), (c), (d), (e), (h), (i), (j), (k), and (l). "May cause drowsiness. Sedatives and tranquilizers may increase the drowsiness effect. Do not give this product to children who are taking sedatives or tranquilizers, without first consulting the child's doctor."

(iii) For products containing diphenhydramine hydrochloride or doxylamine succinate identified in § 341.12 (f) and (g). "May cause marked drowsiness. Sedatives and tranquilizers may increase the drowsiness effect. Do not give this product to children who are taking sedatives or tranquilizers, without first consulting the child's doctor."

(d) * * * * *

(1) For products containing brompheniramine maleate identified in § 341.12 (a). Adults and children 12 years of age and over: oral dosage is 4 milligrams every 4 to 6 hours, not to exceed 24 milligrams in 24 hours, or as directed by a doctor. Children 6 to under 12 years of age: oral dosage is 2 milligrams every 4 to 6 hours, not to exceed 12 milligrams in 24 hours, or as

directed by a doctor. Children under 6 years of age: consult a doctor.

(2) For products containing chlorcyclizine hydrochloride identified in § 341.12 (b). Adults and children 12 years of age and over: oral dosage is 25 milligrams every 6 to 8 hours, not to exceed 75 milligrams in 24 hours, or as directed by a doctor. Children under 12 years of age: consult a doctor.

(3) For products containing chlorpheniramine maleate identified in § 341.12 (c). Adults and children 12 years of age and over: oral dosage is 4 milligrams every 4 to 6 hours, not to exceed 24 milligrams in 24 hours, or as directed by a doctor. Children 6 to under 12 years of age: oral dosage is 2 milligrams every 4 to 6 hours, not to exceed 12 milligrams in 24 hours, or as directed by a doctor. Children under 6 years of age: consult a doctor.

(4) For products containing dexbrompheniramine maleate identified in § 341.12 (d). Adults and children 12 years of age and over: oral dosage is 2 milligrams every 4 to 6 hours, not to exceed 12 milligrams in 24 hours, or as directed by a doctor. Children 6 to under 12 years of age: oral dosage is 1 milligram every 4 to 6 hours, not to exceed 6 milligrams in 24 hours, or as directed by a doctor. Children under 6 years of age: consult a doctor.

(5) For products containing dexchlorpheniramine maleate identified in § 341.12 (e). Adults and children 12 years of age and over: oral dosage is 2 milligrams every 4 to 6 hours, not to exceed 12 milligrams in 24 hours, or as directed by a doctor. Children 6 to under 12 years of age: oral dosage is 1 milligram every 4 to 6 hours, not to exceed 6 milligrams in 24 hours, or as directed by a doctor. Children under 6 years of age: consult a doctor.

(6) For products containing diphenhydramine hydrochloride identified in § 341.12 (f). Adults and children 12 years of age and over: oral dosage is 25 to 50 milligrams every 4 to 6 hours, not to exceed 300 milligrams in 24 hours, or as directed by a doctor. Children 6 to under 12 years of age: oral dosage is 12.5 to 25 milligrams every 4 to 6 hours, not to exceed 150 milligrams in 24 hours, or as directed by a doctor. Children under 6 years of age: consult a doctor.

(7) For products containing doxylamine succinate identified in § 341.12 (g). Adults and children 12 years of age and over: oral dosage is 7.5 to 12.5 milligrams every 4 to 6 hours, not to exceed 75 milligrams in 24 hours, or as directed by a doctor. Children 6 to under 12 years of age: oral dosage is 3.75 to 6.25 milligrams every 4 to 6 hours, not to

exceed 37.5 milligrams in 24 hours, or as directed by a doctor. Children under 6 years of age: consult a doctor.

(8) *For products containing phenindamine tartrate identified in § 341.12(h).* Adults and children 12 years of age and over: oral dosage is 25 milligrams every 4 to 6 hours, not to exceed 150 milligrams in 24 hours, or as directed by a doctor. Children 6 to under 12 years of age: oral dosage is 12.5 milligrams every 4 to 6 hours, not to exceed 75 milligrams in 24 hours, or as directed by a doctor. Children under 6 years of age: consult a doctor.

(9) *For products containing pheniramine maleate identified in § 341.12(i).* Adults and children 12 years of age and over: oral dosage is 12.5 to 25 milligrams every 4 to 6 hours, not to exceed 150 milligrams in 24 hours, or as directed by a doctor. Children 6 to under 12 years of age: oral dosage is 6.25 to 12.5 milligrams every 4 to 6 hours, not to exceed 75 milligrams in 24 hours, or as directed by a doctor. Children under 6 years of age: consult a doctor.

(10) *For products containing pyrilamine maleate identified in § 341.12(j).* Adults and children 12 years of age and over: oral dosage is 25 to 50 milligrams every 6 to 8 hours, not to exceed 200 milligrams in 24 hours, or as directed by a doctor. Children 6 to under 12 years of age: oral dosage is 12.5 to 25 milligrams every 6 to 8 hours, not to exceed 100 milligrams in 24 hours, or as directed by a doctor. Children under 6 years of age: consult a doctor.

(11) *For products containing thonzylamine hydrochloride identified in § 341.12(k).* Adults and children 12 years of age and over: oral dosage is 50 to 100 milligrams every 4 to 6 hours, not to exceed 600 milligrams in 24 hours, or as directed by a doctor. Children 6 to under 12 years of age: oral dosage is 25 to 50 milligrams every 4 to 6 hours, not to exceed 300 milligrams in 24 hours, or as directed by a doctor. Children under 6 years of age: consult a doctor.

(12) *For products containing triprolidine hydrochloride identified in § 341.12(l).* Adults and children 12 years of age and over: oral dosage is 2.5 milligrams every 4 to 6 hours, not to exceed 10 milligrams in 24 hours, or as directed by a doctor. Children 6 to under 12 years of age: oral dosage is 1.25 milligrams every 4 to 6 hours, not to exceed 5 milligrams in 24 hours, or as directed by a doctor. Children under 6 years of age: consult a doctor.

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

8. In Subpart C, § 341.90 (proposed in the Federal Register of January 15, 1985; 50 FR 2200) is amended by redesignating paragraphs (c), (d), (e), (f), (g), (h), (i), (j),

and (k) as paragraphs (d), (e), (f), (g), (i), (j), (k), (l), and (m), and revising them; and by adding new paragraphs (c) and (h) to read as follows:

§ 341.90 Professional labeling.

(c) *For products containing chlorcyclizine hydrochloride identified in § 341.12(b).* Children 6 to under 12 years of age: oral dosage is 12.5 milligrams every 6 to 8 hours, not to exceed 37.5 milligrams in 24 hours. Children 2 to under 6 years of age: oral dosage is 6.25 milligrams every 6 to 8 hours, not to exceed 18.75 milligrams in 24 hours.

(d) *For products containing chlorpheniramine maleate identified in § 341.12(c).* Children 2 to under 6 years of age: oral dosage is 1 milligram every 4 to 6 hours, not to exceed 6 milligrams in 24 hours.

(e) *For products containing dexbrompheniramine maleate identified in § 341.12(d).* Children 2 to under 6 years of age: oral dosage is 0.5 milligram every 4 to 6 hours, not to exceed 3 milligrams in 24 hours.

(f) *For products containing dexchlorpheniramine maleate identified in § 341.12(e).* Children 2 to under 6 years of age: oral dosage is 0.5 milligram every 4 to 6 hours, not to exceed 3 milligrams in 24 hours.

(g) *For products containing diphenhydramine hydrochloride identified in § 341.12(f).* Children 2 to under 6 years of age: oral dosage is 6.25 milligrams every 4 to 6 hours, not to exceed 37.5 mg in 24 hours.

(h) *For products containing doxylamine succinate identified in § 341.12(g).* Children 2 to under 6 years of age: oral dosage is 1.9 to 3.125 milligrams every 4 to 6 hours, not to exceed 18.75 milligrams in 24 hours.

(i) *For products containing phenindamine tartrate identified in § 341.12(i).* Children 2 to under 6 years of age: oral dosage is 6.25 milligrams every 4 to 6 hours, not to exceed 37.5 milligrams in 24 hours.

(j) *For products containing pheniramine maleate identified in § 341.12(j).* Children 2 to under 6 years of age: oral dose is 3.125 to 6.25 milligrams every 4 to 6 hours, not to exceed 37.5 milligrams in 24 hours.

(k) *For products containing pyrilamine maleate identified in § 341.12(j).* Children 2 to under 6 years of age: oral dosage is 6.25 to 12.5 milligrams every 6 to 8 hours, not to exceed 50 milligrams in 24 hours.

(l) *For products containing thonzylamine hydrochloride identified in § 341.12(k).* Children 2 to under 6 years of age: oral dosage is 12.5 to 25 milligrams every 4 to 6 hours, not to exceed 150 milligrams in 24 hours.

(m) *For products containing triprolidine hydrochloride identified in § 341.12(l).* Children 4 to under 6 years of age: oral dosage is 0.938 milligram every 4 to 6 hours, not to exceed 3.744 milligrams in 24 hours. Children 2 to under 4 years of age: oral dosage is 0.625 milligram every 4 to 6 hours, not to exceed 2.5 milligrams in 24 hours. Infants 4 months to under 2 years of age: oral dosage is 0.313 milligram every 4 to 6 hours, not to exceed 1.252 milligrams in 24 hours.

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

9. The authority citation for 21 CFR Part 369 is revised 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]

10. In Subpart B, § 369.20 *Drugs; recommended warning and caution statements* is amended by removing the reference to paragraph (a)(25) of § 310.201 from the entry "ANTIHISTAMINICS, ORAL," and by removing the paragraph "Cyclizine-containing preparations should include the following:" and the "Warning" statement following that paragraph.

§ 369.21 [Amended]

11. In Subpart B, § 369.21 *Drugs; warning and caution statements required by regulations* is amended by removing the reference to paragraph (a)(25) of § 310.201 and by removing "DOXYLAMINE SUCCINATE" and "CHLORCYCLIZINE HYDROCHLORIDE" from the entry "ANTIHISTAMINICS, ORAL (PHENYLTOLOXAMINE DIHYDROGEN CITRATE, MECLIZINE HYDROCHLORIDE, DOXYLAMINE SUCCINATE, CHLOROTHEN CITRATE, CYCLIZINE HYDROCHLORIDE, AND CHLORCYCLIZINE HYDROCHLORIDE," and by removing the paragraph "For chlorcyclizine-, cyclizine-, or meclizine-containing preparations, the statement:" and the "Warning" statement following that paragraph.

Dated: May 31, 1987.

Frank E. Young,

Commissioner of Food and Drugs.

[FR Doc. 87-19062 Filed 8-21-87; 8:45 am]

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