DEPARTMENT OF HEALTH AND HUMAN SERVICES

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[Docket Nos. 1976N–0052N (formerly 1976N–052N) and 1981N–0022 (formerly 81N–0022)]

RIN 0910–AF34, 0910–AF45

Phenylpropanolamine-Containing Drug Products for Over-the-Counter Human Use; Tentative Final Monographs

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice of proposed rule.

SUMMARY: The Food and Drug Administration (FDA) is issuing a notice of proposed rulemaking (notice) for over-the-counter (OTC) nasal decongestant and weight control drug products containing phenylpropanolamine preparations. This proposed rule reclassifies phenylpropanolamine preparations from their previously proposed monograph status (Category I) for these uses to nonmonograph (Category II) status based on safety concerns. FDA is issuing this proposed rule after considering new data and information on the safety of phenylpropanolamine as part of its ongoing review of OTC drug products.

DATES: Submit written and electronic comments and new data by [*insert date 90 days after date of publication in the* **Federal Register**]. Written and electronic comments on the agency's economic impact determination by [*insert date 90 days after date of publication in the* **Federal Register**]. Please see

NPR4

section X of this document for the effective date of any final rule that may be published based on this proposal.

ADDRESSES: You may submit comments, identified by Docket Nos. 1976N–0052N and 1981N–0022 and/RIN number 0910–AF34 and 0910–AF45, by any of the following methods:

Electronic Submissions

Submit electronic comments in the following ways:

- Federal eRulemaking Portal: *http://www.regulations.gov.* Follow the instructions for submitting comments.
- Agency Web site: *http://www.fda.gov/dockets/ecomments.* Follow the instructions for submitting comments on the agency Web site.

Written Submissions

Submit written submissions in the following ways:

- FAX: 301–827–6870.
- Mail/Hand delivery/Courier [For paper, disk, or CD–ROM submissions]: Division of Dockets Management (HFA–305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852.

To ensure more timely processing of comments, FDA is no longer accepting comments submitted to the agency by e-mail. FDA encourages you to continue to submit electronic comments by using the Federal eRulemaking Portal or the agency Web site, as described in the *Electronic Submissions* portion of this paragraph.

Instructions: All submissions received must include the agency name and Docket No(s). and Regulatory Information Number (RIN) (if a RIN number has been assigned) for this rulemaking. All comments received may be posted without change to *http://www.fda.gov/ohrms/dockets/default.htm*, including

any personal information provided. For detailed instructions on submitting comments and additional information on the rulemaking process, see the "Comments" heading of the **SUPPLEMENTARY INFORMATION** section of this document.

Docket: For access to the docket to read background documents or comments received, go to *http://www.fda.gov/ohrms/dockets/default.htm* and insert the docket number(s), found in brackets in the heading of this document, into the "Search" box and follow the prompts and/or go to the Division of Dockets Management, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852.

FOR FURTHER INFORMATION CONTACT: Gerald M. Rachanow or Robert L. Sherman, Center for Drug Evaluation and Research, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 22, rm. 5426, Silver Spring, MD 20993, 301–796–2090.

SUPPLEMENTARY INFORMATION:

I. Background

In the **Federal Register** of September 9, 1976 (41 FR 38312), FDA published an advance notice of proposed rulemaking (ANPR) under 21 CFR 330.10(a)(6) 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). This Panel was the advisory review panel responsible for evaluating data on the active ingredients in these drug classes. This Panel recommended monograph (Category I) status for phenylpropanolamine preparations (phenylpropanolamine bitartrate, phenylpropanolamine hydrochloride, and phenylpropanolamine maleate) as an oral nasal decongestant.

In the **Federal Register** of February 26, 1982 (47 FR 8466), FDA published an ANPR to establish a monograph for OTC weight control drug products, together with the recommendations of the Advisory Review Panel on OTC Miscellaneous Internal Drug Products (Miscellaneous Internal Panel). This Panel was the advisory review panel responsible for evaluating data on the active ingredients in this drug class. This Panel recommended monograph status for phenylpropanolamine hydrochloride for weight control use. However, after the Panel submitted its report, FDA became aware of and discussed studies indicating that certain dosages of phenylpropanolamine cause blood pressure elevation (47 FR 8466). Therefore, in the preamble to the Panel's report, FDA specifically requested data and information on the extent to which phenylpropanolamine induces or aggravates hypertension (47 FR 8466 at 8468).

In the **Federal Register** of January 15, 1985 (50 FR 2220), FDA published a proposed regulation for OTC nasal decongestant drug products in the form of a tentative final monograph. Because the issues concerning the safety of phenylpropanolamine for nasal decongestant and weight control use were closely related, FDA stated in that document that it was deferring phenylpropanolamine and would consider the issues concurrently in a future **Federal Register** publication (50 FR 2220 at 2221).

Phenylpropanolamine was not included in the October 30, 1990 (55 FR 45788), proposed rule or the August 8, 1991 (56 FR 37792), final rule for OTC weight control drug products, in which 111 weight control active ingredients were determined to be nonmonograph. Benzocaine and phenylpropanolamine hydrochloride, the two ingredients the Miscellaneous Internal Panel classified as Category I, were deferred to a future publication. The current document

addresses phenylpropanolamine. FDA will discuss benzocaine for weight control use in a future issue of the **Federal Register**.

In a letter to the Nonprescription Drug Manufacturers Association dated March 9, 1993 (Ref. 1), FDA stated that, based on a relatively small number of spontaneous reports of intracranial bleeding associated with weight control drug products containing phenylpropanolamine, FDA's principal safety concern was the possibility that phenylpropanolamine might increase the risk of stroke. FDA further stated that although the available data could not support a conclusion that phenylpropanolamine increased the rate of strokes, these data could not rule out the possibility of an increased stroke risk associated with OTC phenylpropanolamine use.

Phenylpropanolamine preparations also were not included in the final rule for OTC nasal decongestant drug products that published in the **Federal Register** of August 23, 1994 (59 FR 43386). FDA stated that because of still unresolved safety issues concerning phenylpropanolamine preparations, it was deferring action on this drug (59 FR 43386).

In the **Federal Register** of February 14, 1996 (61 FR 5912), FDA published a proposed regulation requiring new warning labeling for all OTC phenylpropanolamine preparations. In that document, FDA stated that dose-response studies submitted by drug manufacturers to investigate phenylpropanolamine's effects on blood pressure were inadequate to alleviate FDA's concern that phenylpropanolamine used in OTC drug products might increase the risk of hemorrhagic stroke.

Spontaneous case reports and published case series accumulated from 1969 to 1991 suggested a possible association between phenylpropanolamine use and an increased risk of hemorrhagic stroke. Thus, the status of

phenylpropanolamine had been deferred pending further study. In an effort to resolve these issues, representatives of the manufacturers of products containing phenylpropanolamine and FDA staff met in 1991 to plan a study that could further examine whether there was an association between phenylpropanolamine use and risk of hemorrhagic stroke. An epidemiologic case-control study was determined to be the most feasible study design to evaluate the possible association between exposure to phenylpropanolamine and a rare outcome such as hemorrhagic stroke. The industry sponsors of the study selected investigators at Yale University School of Medicine to conduct the study. The Yale investigators submitted protocols to FDA for review. The results of the study are discussed in section II of this document.

In this proposed rule, FDA proposes to categorize all phenylpropanolamine preparations as nonmonograph (Category II) for OTC use in both nasal decongestant and weight control drug products. This action is based on reports published in the medical literature, FDA's initial review of adverse drug event reports associated with OTC phenylpropanolamine drug products between 1969 and 1991, continuing adverse drug event reports since 1991, and the results of the Yale Hemorrhagic Stroke Project (Ref. 2). Because safety concerns are the basis for this proposed nonmonograph status, FDA does not address the effectiveness of phenylpropanolamine preparations in this document.

II. Data on the Safety of Phenylpropanolamine from the Yale Hemorrhagic Stroke Project

A. Introduction and Rationale

The following discussion was developed from the study report (Ref. 2) submitted to FDA.

The Yale Hemorrhagic Stroke Project (Ref. 2) was a case-control study. Because several case reports had involved strokes in young women who took phenylpropanolamine as an appetite suppressant, often after a first dose, the study examined three questions: (1) Whether all users of phenylpropanolamine, compared to nonusers, had an increased risk of hemorrhagic stroke, (2) the possible association between phenylpropanolamine and hemorrhagic stroke by type of exposure (appetite suppressant or cough-cold product), and (3) among women age 18 to 49 years, the possible association between first use of phenylpropanolamine and hemorrhagic stroke and the possible association between use of phenylpropanolamine-containing appetite suppressants and hemorrhagic stroke.

The study was performed between December 1994 and July 1999 and involved men and women 18 to 49 years old who were hospitalized with a primary subarachnoid hemorrhage (SAH) or a primary intracerebral hemorrhage (ICH) (unrelated to ischemic infarction, trauma, cerebral thrombosis, or thrombolytic therapy). The subjects were recruited from 44 hospitals in 4 geographic regions of the United States.

Both SAH and ICH were determined by clinical symptoms and specific diagnostic information from computed tomography. Magnetic resonance imaging was accepted for the diagnosis of SAH or ICH only if other procedures were not diagnostic. Because misclassification of exposure status by surrogate responders could increase or reduce the observed odds ratio and the true level of risk (Ref. 2), subjects were ineligible for enrollment if they died (n=389) or were not able to communicate (n=194) within 30 days after their event. Subjects were also ineligible if they had a previously diagnosed brain lesion predisposing to hemorrhage risk (e.g., arteriovenous malformation, vascular

aneurysm, or tumor) (n=48), a prior stroke (n=120), or first experienced stroke symptoms after being in the hospital for 72 hours (e.g., for an unrelated matter) (n=33).

For each case subject, random digit dialing (matched to the first three digits of the case subject's telephone number) was used to identify two control subjects who were matched on : (1) Gender, (2) race (African-American versus non-African-American), (3) age (within 3 years for case subjects less than 30 years and within 5 years for subjects 30 years or over), (4) educational level, and (5) telephone exchange (as a surrogate for socioeconomic status). Case subjects and control subjects were interviewed to ascertain medical history, medication use, and habits affecting health, such as use of tobacco and alcohol. Interviews of control subjects were completed within 30 days of the case subject's stroke event to minimize seasonal differences in the likelihood of exposure to cough-cold drug products. Eligibility criteria for control subjects were the same as for case subjects except for the stroke event. During the consent procedure, all subjects (cases and controls) were told that the study was designed to examine causes of hemorrhagic stroke in young persons without specific mention of phenylpropanolamine or other potential risk factors. Case and control subjects were interviewed by a trained interviewer using a structured questionnaire developed for this study. Reported phenylpropanolamine exposures were verified by the study investigators, who documented the actual product(s) used and their ingredients.

A focal time (the calendar day and the time of onset of symptoms plausibly related to hemorrhagic stroke that caused a subject to seek medical help) was identified for each case subject. The focal time used for each control subject was matched to the day of the week and the time of day that corresponded

to the case subject's focal time. Control subjects were interviewed within 7 days of their focal time to minimize recall bias.

The exposure window referred to the interval before the focal time (onset of symptoms) when the status of a subject's exposure to phenylpropanolamine was defined. For analyses other than those involving first use of phenylpropanolamine, the exposure window was defined as 4 days preceding the focal time. For first use of phenylpropanolamine, the exposure window was within 24 hours before the focal time, provided that the subject had not used any other phenylpropanolamine products during the preceding 2 weeks. To maintain a consistent reference group, nonexposure for all analyses was defined as no use of phenylpropanolamine within 2 weeks before the focal time. Exposure windows for control subjects were matched to those for the corresponding case subjects.

B. Statistical Analysis

Case and control subjects were compared on a variety of clinical and demographic features, including those used in matching, to determine the comparability of the two groups. Statistical comparisons were made using chi-square tests and the Fisher's exact test (where appropriate) for categorical variables, and the Student t-test for continuous variables. For the analyses of the primary endpoints, conditional logistic models for matched sets (with a variable number of controls per case) were used to estimate odds ratios, lower limits of the one-sided 95 percent confidence intervals, and p-values for the risk factors under investigation. One-tailed statistical results were reported because the focus of the study was whether phenylpropanolamine use increased the risk of stroke and this was the pre-specified analysis. Each logistic model was estimated with two mutually exclusive binary exposure

terms: (1) The subject's primary exposure status as defined by the specific aim (e.g., phenylpropanolamine use in the 3-day window; yes/no), and (2) phenylpropanolamine users who were not exposed within the 3-day window (but with some exposure within 2 weeks of the focal time).

In multivariate conditional logistic models (using asymptotic methods), adjustments were made for race (African-American compared with non-African-American), history of hypertension (yes/no), and current cigarette smoking (current compared with never or ex-smoker) because these are the major risk factors for stroke. Other underlying diseases and/or conditions (i.e. diabetes, polycystic kidney disease, congestive heart failure, sickle cell anemia, and clotting disorders) were also examined to determine if any of them, when added to this basic adjusted model, altered the matched odds ratio by at least 10 percent.

C. Study Results

There were 702 case subjects, including 425 subjects (60 percent) with an SAH and 277 (40 percent) with an ICH, and 1,376 control subjects. Hemorrhage was associated with an aneurysm in 307 subjects (44 percent), an arteriovenous malformation in 50 subjects (7 percent), and a tumor in one subject (0.1 percent). Two control subjects were located for each of 674 case subjects (96 percent) and one control subject for each of 28 case subjects (4 percent). All control subjects were matched to their case subjects on gender and telephone exchange. Age matching was successful for 1,367 controls (99 percent) and race matching was achieved for 1,321 controls (96 percent). Twenty-seven case subjects and 33 control subjects reported phenylpropanolamine use within the 3-day exposure window.

Compared to control subjects, case subjects were significantly more likely to be African-American (21 percent compared with 17 percent). Case subjects were also more likely to report lower educational achievement (20 percent did not graduate from high school compared with 9 percent of control subjects), current cigarette smoking (51 percent compared with 30 percent), a history of hypertension (39 percent compared with 20 percent), family history of hemorrhagic stroke (9 percent compared with 5 percent), heavy alcohol use (14 percent compared with 7 percent), and recent cocaine use (2 percent compared with less than 1 percent). For all other clinical variables examined, case and control subjects were not dissimilar. Case subjects were significantly (0.05) less likely to report use of nonsteroidal anti-inflammatory drugs and significantly more likely to report use of caffeine and nicotine in the 3 days before their event. Of the factors examined, only education changed the adjusted odds ratio for the association between phenylpropanolamine and hemorrhagic stroke by more than 10 percent, and this demographic factor was included in all subsequent models.

Analyses of the study results demonstrated an association between hemorrhagic stroke and use of phenylpropanolamine (in both nasal decongestant and weight control drug products) in the 3 days prior to the event. Such use of phenylpropanolamine, compared to no use in the prior 2 weeks, was associated with a relative risk for hemorrhagic stroke of 1.67 (unadjusted odds ratio) (p=0.040). The corresponding adjusted odds ratio was 1.49 (lower limit of the one-sided 95 percent confidence interval (LCL)=0.93, p=0.084).

The relative risks of hemorrhagic stroke observed with use of the two types of phenylpropanolamine-containing products (in the 3–day exposure window,

compared to no use in the prior 2 weeks) were as follows. For cough-cold products, the unadjusted odds ratio was 1.38 (p=0.163) and the adjusted odds ratio (AOR) was 1.23 (LCL=0.75, p=0.245). For weight control products, the unadjusted odds ratio was 11.98 (p=0.007) and the AOR was 15.92 (LCL=2.04, p=0.013).

To analyze the relation between recency of phenylpropanolamine exposure and risk for hemorrhagic stroke, odds ratios were also calculated according to the timing of the most recent phenylpropanolamine use. The pre-specified definition for current use was use of any phenylpropanolamine-containing product on the day of the event (before focal time) or the preceding calendar day. Prior use was defined as use 2 or 3 calendar days before the focal time. The odds ratio was slightly higher for current use (AOR=1.61, LCL=0.93, p=0.078) than for prior use (AOR=1.16, LCL=0.47, p=0.393). Within current use, odds ratios were then calculated according to first use or non-first use. First use was defined as current use with no other use within the prior 2 weeks. Non-first use included other uses within the 2–week interval. The odds ratio was higher for first use (AOR=3.14, LCL=1.16, p=0.029) than for non-first use (AOR=1.20, LCL=0.61, p=0.329). All first uses of phenylpropanolamine (n=13) reported in these data were in cough-cold products.

In women using phenylpropanolamine in weight control drug products (3–day exposure window, versus no use in the prior 2 weeks), the unadjusted odds ratio for hemorrhagic stroke was 12.19 (p=0.006) and the AOR was 16.58 (LCL=2.22, p=0.011). All hemorrhagic stroke events that occurred within the 3-day exposure window were in women. In the analyses of the association between hemorrhagic stroke and first-day use of phenylpropanolamine, 11 of

the 13 first-day use events were in women (7 cases compared with 4 controls). The unadjusted odds ratio was 3.50 (p=0.039) and the AOR was 3.13 (LCL=1.05, p=0.042).

Based on the findings that risk for hemorrhagic stroke seemed to be concentrated among current users, the association between current phenylpropanolamine dose and risk for hemorrhagic stroke was examined. Among 21 exposed control subjects, the median current dose of phenylpropanolamine (i.e., total amount taken on the index day or preceding day) was 75 milligrams (mg). Analysis according to dose shows that the odds ratio was higher for current doses above the median (greater than 75 mg) (AOR=2.31, LCL=1.10, p=0.031) than for lower doses (AOR=1.01, LCL=0.43, p=0.490). Among first-dose users, four of eight cases and two of five controls were exposed to greater than 75 mg of phenylpropanolamine. To examine the potential effect of ambiguity in the correct focal time, the odds ratios were recalculated after excluding all 154 case subjects who were classified as having a definite (n=76) or uncertain (n=78) sentinel symptom preceding the stroke event. The magnitude of the AORs did not change substantially.

D. Study Conclusions

According to the investigators, several features of the study supported the validity of the study findings regarding a demonstrated association between phenylpropanolamine use and risk of hemorrhagic stroke in subjects between 18 and 49 years of age. First, in addition to the finding of elevated odds ratios that reached statistical significance, the magnitude of the odds ratios for phenylpropanolamine use as an appetite suppressant (15.92) and as a first-dose use (3.14) remained large even after adjustment for important clinical features. Second, the data demonstrate an association between both types of

phenylpropanolamine drug products (nasal decongestant and weight control) and hemorrhagic stroke. Because so few men were exposed to phenylpropanolamine in this study (n=19), it was not possible to determine whether their risk for hemorrhagic stroke (when using phenylpropanolamine) is different from that of women.

E. FDA's Evaluation of the Study

Observational studies, particularly case-control studies, are potentially subject to a number of biases, and this case-control study is no exception. The hallmark of a good case-control study is that biases are anticipated and measures are instituted in the design and analysis stages to minimize biases to the greatest extent possible.

Strict diagnostic criteria, as described previously, were developed to ensure accurate identification of hemorrhagic stroke cases in the target population. A number of steps were taken to minimize misclassification bias. One of the investigators confirmed the stroke by reviewing the medical records of suspected cases, without knowledge of the exposure status. Inclusion and exclusion criteria were clearly defined for both cases and controls. Exposure was clearly defined, an exposure window was identified, and exposure was ascertained by trained interviewers. Interviewers were randomly assigned to cases or controls, and questions were asked about multiple medications, thus blinding subjects to the exact exposure under study. The interviews were highly structured and scripted to protect against interviewer bias. Because phenylpropanolamine use might be seasonal, controls were identified and interviewed within 30 days of the date of their matched case subject's stroke, to ensure that cases and controls had similar opportunities for exposure. Controls were also matched to cases for day of the week and time of day of

the stroke. This matching strategy helped increase the probability that exposure to any seasonal medication or other covariates (e.g., alcohol drinking or cigarette smoking) was similar between cases and controls.

The investigators attempted to identify two controls per case by using random digit dialing (with a match for the first three digits of the telephone number). Because controls were population-based, the results were generalizable to the source population from which the cases and controls were drawn. Matching on race and educational level was slightly unequal between cases and controls. The investigators further controlled for these inequalities by adjustment during analysis. The agency concludes that matching was largely successful.

The investigators reduced the possibility of misclassification of phenylpropanolamine use by using a highly structured questionnaire. Each reported medication was verified by asking subjects to present the actual container or by picking out reported brand-name medications from a book containing photographs. Verification of medication use in the 3-day window prior to the focal time was 96 and 94 percent for cases and controls, respectively. The investigators conducted two additional steps to further ensure that the possibility of exposure misclassification error was reduced to an absolute minimum: (1) Only "definite" and "possible" exposure responses were considered in the analyses, and (2) the use of other OTC drugs between cases and controls were compared to ensure that the cases did not have greater recall of the use of any drugs as a reason for their stroke. Based on this analysis, FDA did not find any evidence of recall or misclassification bias.

Several key elements of study design and conduct determine the success of a case-control study. Studies must have adequate sample size and/or power

to detect a difference between treatment groups if a difference really exists, and detection of rare events can require substantial numbers of study subjects. FDA had concerns that the protocol might result in an underpowered study because the sample size calculation was based on an odds ratio of five for an association between first-day use of phenylpropanolamine and hemorrhagic stroke. This ratio was derived primarily from study conduct considerations, such as time and cost, rather than on predictive epidemiologic data that may have suggested that a greater number of subjects would be needed to show a difference between groups. Because case-control studies also demand adherence to strict matching criteria between case and control subjects, the duration of this study was longer than expected due to difficulties in recruiting well-matched controls.

The resultant study was the largest prospective case-control study ever conducted on hemorrhagic stroke. FDA finds that, despite these limitations, this study was well-conducted and the statistical analyses demonstrate an association between phenylpropanolamine and hemorrhagic stroke, as explained as follows.

FDA notes that the three most important risk factors (race, history of hypertension, and cigarette smoking) were included in the multivariate analysis (basic adjusted model). The confounding effect of the other covariates was examined if adding any of them to the basic model altered the odds ratio estimate by 10 percent. High school education was the only covariate determined to change the odds ratio by at least 10 percent.

Because the study had a matched design, FDA considers the conditional logistic regression model appropriate to calculate both unadjusted and AORs. In addition, the number of exposures was small, particularly for analysis of

appetite suppressant and first use, thus, the authors calculated the confidence interval of the unadjusted odds ratio based on an exact method.

Hypertension is the single most important risk factor for a stroke. Misclassification of hypertension status could result in residual confounding. FDA examined the possible effects of this residual confounding on the results of the study. FDA found that the odds ratio for appetite suppressant use was 15.92, a substantial increase in risk. Its very magnitude makes it difficult to explain by confounding alone. Because product labeling advises hypertensive persons to avoid phenylpropanolamine use, the association of phenylpropanolamine use with hypertension should be negative. Such a negative association would result in biasing the result towards no association if the confounding factor is not controlled for. In addition to the steps taken by the investigators, FDA examined this further by additional analyses restricted to subjects without a past history of hypertension, and the results were not significantly different, thereby providing additional evidence that confounding by hypertension was not present in the study.

FDA requested the Yale investigators to explore the possible impact of cigarette smoking and alcohol consumption in more detail. The investigators found that the odds ratios for phenylpropanolamine and stroke were essentially unchanged by inclusion of several qualitative and quantitative measures of smoking and alcohol consumption.

The investigators examined the association between current phenylpropanolamine dose and risk for hemorrhagic stroke. Among 21 exposed control subjects, the median current dose of phenylpropanolamine (i.e., the total amount taken on the index day or preceding day) was 75 mg. The AOR was higher for current doses above 75 mg than for lower doses.

Among first dose users, four of eight cases and two of five controls were exposed to greater than 75 mg of phenylpropanolamine. As 75 mg is a single dose of many OTC extended-release phenylpropanolamine cough-cold drug products with recommended adult dosing every 12 hours (150 mg a day), the agency further evaluated the association between risk of hemorrhagic stroke and a range of current phenylpropanolamine doses. Exploratory analyses suggest that there may be an increased risk of hemorrhagic stroke with labeled doses at or above 75 mg a day. Although not statistically significant, a trend toward a dose-ordering of odds ratios was seen. The odds ratio was higher (AOR=2.31, LCL=1.10, p=0.031) for current doses above 75 mg than for doses below 75 mg (AOR=1.01, LCL=0.43, p=0.490).

FDA concludes that the Yale study (Ref. 2) was well-designed and demonstrated an association between use of phenylpropanolamine and an increased risk of hemorrhagic stroke. The increased risk was most striking in women and was associated with both use in appetite suppressants and first-dose use in cough-cold products. The case-control design was best suited for this study because the outcome under investigation was rare. The investigators took reasonable steps to minimize bias and confounding and built quality control measures into the study design. Analysis was appropriate for the type of study and was performed according to the protocol. The study had clear objectives and sound epidemiology practices were used in its design and execution.

F. Additional Reports

FDA reviewed its adverse events reporting system for spontaneous reports of hemorrhagic stroke from 1991 to 2000 and identified 22 cases, 16 in the 18 to 49 age group with 13 cases in women (Ref. 3). In all cases, the suspect

drug was an extended-release product containing 75 mg of phenylpropanolamine per unit dose. Of 11 cases for which the indication for use was provided, 10 reported use for respiratory symptoms. FDA believes that the fact that there were no reports associated with immediate release drug products marketed under the OTC drug monograph system may be related to the lack of a requirement to submit any such reports to the agency.

Therefore, the absence of such reports does not indicate these products are not associated with adverse events.

G. Advisory Committee Recommendations

On October 19, 2000, at a public meeting, FDA presented to its Nonprescription Drugs Advisory Committee (NDAC) the regulatory history of OTC phenylpropanolamine (including FDA's concerns about case reports of hemorrhagic stroke associated with phenylpropanolamine prior to 1991), the data from the Yale Hemorrhagic Stroke Project, and additional case reports of stroke since 1991.

The Yale investigators presented the study results and their conclusions. Industry representatives raised concerns about the design of the study that they believed made interpretation of the results difficult (Ref. 4). NDAC evaluated whether the Yale study showed an association between phenylpropanolamine use and an increased risk of stroke in different populations aged 18 to 49 (female, male, both) and for different uses (nasal decongestant, appetite suppressant, all) (Ref. 5). More importantly, NDAC was asked if the data support the conclusion that there is an association between phenylpropanolamine and an increased risk of hemorragic stroke, taking into account all currently available information, including: (1) Phenylpropanolamine's effects on blood pressure, (2) spontaneous reports of

hemorrhagic stroke associated with phenylpropanolamine from 1969 to 1991, (3) case reports in the medical literature, (4) continuing adverse drug reports to FDA from 1991 to the present, and (5) the results of the Yale Hemmorhagic Stroke Project. Thirteen of 14 NDAC members voted (with 1 voting "uncertain") that there is such an association (Ref. 5). When asked whether phenylpropanolamine can be generally recognized as safe for use as a nasal decongestant, 12 of the 14 NDAC members voted (with 2 abstaining) that phenylpropanolamine could not be considered to be generally recognized as safe for OTC nasal decongestant use. In addition, when asked whether phenylpropanolamine can be generally recognized as safe for use as an appetite suppressant, 13 of the 14 NDAC members voted (with 1 abstaining) that phenylpropanolamine could not be considered to be generally recognized as safe for OTC weight control use.

III. FDA's Tentative Conclusions on the Safety of Phenylpropanolamine

FDA believes that the known scientific evidence supports the conclusion that nasal decongestant and weight control drug products containing phenylpropanolamine cannot be generally recognized as safe and should no longer be available for OTC use. This evidence includes the results of the Yale study suggesting an association between phenylpropanolamine and hemorrhagic stroke, previous and continuing adverse event reports, reports in the published medical literature, and the biological plausibility related to phenylpropanolamine's ability to cause increases in blood pressure. As stated in section II.E of this document, FDA concludes that the Yale study (Ref. 2) was well-designed and demonstrated an association between use of phenylpropanolamine and an increased risk of hemorrhagic stroke. The increased risk was most striking in women and was associated with both use

in appetite suppressants and first-dose use in cough-cold products. The case-control design was best suited for this study because the outcome under investigation was rare. The investigators took reasonable steps to minimize bias and confounding and built quality control measures into the study design. Analysis was appropriate for the type of study and was performed according to the protocol. The study had clear objectives and sound epidemiology practices were used in its design and execution. Regardless of the analytic methods used, the findings were consistent.

Although the Yale study focused on men and women 18 to 49 years of age, FDA has no data to show that the increased risk of hemorrhagic stroke is limited to a specific age range. While the Yale study was being conducted, FDA received spontaneous reports of hemorrhagic stroke in people 28 to 54 years of age with cough-cold products that contain OTC doses of phenylpropanolamine.

Because the factors that may cause some individuals to be particularly sensitive to the effects of phenylpropanolamine are unknown, individuals at risk cannot be adequately warned through labeling. Although there is no other active ingredient that is generally recognized as safe and effective for OTC weight control use, OTC nasal decongestant drug products can be reformulated with other ingredients, such as pseudoephedrine and phenylephrine. Because hemorrhagic strokes often lead to catastrophic, irreversible outcomes, FDA concludes that the benefits of the intended uses of phenylpropanolamine do not outweigh the potential risk, and that phenylpropanolamine is not considered to be generally recognized as safe.

IV. Analysis of Impacts

FDA has examined the impacts of this proposed rule under Executive Order 12866, the Regulatory Flexibility Act (5 U.S.C. 601–612), and the Unfunded Mandates Reform Act of 1995 (2 U.S.C. 1501 *et seq.*). Executive Order 12866 directs agencies to assess all costs and benefits of available regulatory alternatives and, when regulation is necessary, to select regulatory approaches that maximize net benefits (including potential economic, environmental, public health and safety, and other advantages; distributive impacts; and equity). Under the Regulatory Flexibility Act, if a rule might have a significant economic impact on a substantial number of small entities, an agency must consider alternatives that would minimize any significant economic impact of the rule on small entities. Section 202(a) of the Unfunded Mandates Reform Act of 1995 requires that agencies prepare a written statement of anticipated costs and benefits before proposing any rule that may result in an expenditure by state, local, and tribal governments, in the aggregate, or by the private sector, of $100 million (adjusted annually for inflation) in any one year.

FDA tentatively concludes that this proposed rule is consistent with the principles set out in Executive Order 12866 and in these two statutes. As shown as follows, FDA does not believe the proposed rule will be economically significant as defined by the Executive order. Based on its preliminary Regulatory Flexibility Analysis, FDA tentatively concludes that this proposed rule would not impose a significant economic impact on a substantial number of small entities. The Unfunded Mandates Reform Act of 1995 does not require FDA to prepare a statement of costs and benefits for the proposed rule, because the proposed rule is not expected to result in an

expenditure that would exceed $100 million adjusted for inflation in any one year. The current inflation-adjusted statutory threshold is about $110 million.

The purpose of the proposed rule is to establish that phenylpropanolamine preparations are not generally recognized as safe for OTC use both as a nasal decongestant and for weight control. This proposed rule would assure the removal of OTC drug products containing phenylpropanolamine, if any are still marketed, and prohibit future marketing of such products.

FDA believes that the benefits of this rule justify the costs. Our estimate of the benefits of complete elimination of phenylpropanolamine preparations suggests that they could be as high as $250 million to $625 million annually, if estimated using a willingness to pay approach. The vast majority of these benefits are not directly attributable to this rule, however, because industry previously took voluntary action to discontinue production and marketing of phenylpropanolamine preparations.

Similarly, most costs of product withdrawal or reformulation have already been incurred because of the voluntary actions. However, a few affected products may still be available and products that have been withdrawn could still, in principle, be reintroduced in the absence of the rule. Any remaining products containing phenylpropanolamine will need to cease OTC marketing upon the effective date of any final rule, but can be reformulated with another ingredient, where applicable. Products that are reformulated will also need to be relabeled.

A. Background for Analysis of Impact

In November 2000, FDA issued a public health advisory on the safety of phenylpropanolamine and announced that it would take steps to remove phenylpropanolamine from all drug products and had requested all drug

companies to voluntarily discontinue marketing products containing phenylpropanolamine (Ref. 6). As a result of this announcement and the publication of the Yale Hemorrhagic Stroke Project, national chain drugstore and major and smaller manufacturers voluntarily removed phenylpropanolamine-containing OTC drug products from the market. Manufacturers of phenylpropanolamine-containing OTC drug products were aware of the potential health problem and some manufacturers of OTC nasal decongestant drug products containing phenylpropanolamine had already reformulated or were in the process of reformulating their products to remove phenylpropanolamine in advance of FDA's announcement. Nevertheless, a number of factors markedly accelerated this trend:

- The recommendation of FDA's NDAC
- The publication of the results of the Yale Hemorrhagic Stroke Project
- FDA's subsequent announcement of its intent to reclassify phenylpropanolamine as a Category II ingredient, and FDA's request for a voluntary recall.

These events led to the voluntary removal from the market of most remaining phenylpropanolamine-containing OTC drug products. Both market forces (i.e., avoidance of tort liability) and FDA's request for a voluntary recall contributed to the decision by retail establishments and manufacturers to discontinue sales. Because public awareness, market forces, and FDA's announcement and request to voluntarily withdraw occurred within a short span of time, it is not possible for FDA to disentangle the impact these various factors had on manufacturers' decisions to voluntarily recall phenylpropanolamine drug products.

OMB guidelines on economic impact analyses direct agencies to estimate costs and benefits from an appropriate baseline. "This baseline should be the best assessment of the way the world would look absent the proposed regulation" (Ref. 7). We do not believe that the conditions prior to FDA's announcement of its intent to classify this ingredient as nonmonograph are the appropriate baseline because the publication of the Yale Hemorrhagic Stroke Project in a leading medical journal alone would have generated a market response. We acknowledge that the timing and wording of FDAs public announcement and request for voluntary recalls contributed to the magnitude of the incurred costs. However, because the costs attributable to the withdrawal of phenylpropanolamine-containing OTC drug products have already occurred, and may have occurred absent this proposed rule, albeit at a slower pace, FDA believes present conditions are the appropriate baseline from which to estimate the impact of this proposed rule.

Even if all of these costs were attributed to this proposed rule, however, they would not rise to the $100 million per year threshold sufficient to categorize this rule as economically significant under section 3.f. of E.O. 12866. Nonetheless, we account for as much of the cost as possible using 2000 as the baseline year for the number of affected products

B. Costs of Regulation

a. *Costs of removing products from the market.* FDA finds that a number of affected firms incurred substantial costs from these voluntary product withdrawals. In addition, we are not aware of any phenylpropanolamine-containing OTC drug products currently marketed, so we believe the removal-related costs have already been incurred.

The voluntary product withdrawals primarily affected two major OTC drug markets—weight control and cough-cold medications. The weight control drug products sector reported $48 million in annual sales for phenylpropanolamine-containing drug products in 2000. The much larger cough-cold products sector had total sales of about $1.2 billion (Ref. 8), but FDA does not have an estimate of the proportion of this figure that included only phenylpropanolamine-containing products. As a result, FDA cannot estimate the total sales of all OTC drug product lines that contained phenylpropanolamine.

In 2000, FDAs drug listing system included approximately 400 drug products containing phenylpropanolamine, with approximately 100 manufacturers and 250 distributors and repackers. Many of the 400 products were marketed by distributors and hence do not represent unique formulations. FDA estimates that there may have been around 150 distinct products for both cough-cold and weight loss. Not all of these products, however, were reformulated. Some manufacturers had already added product lines containing a substitute active ingredient and had no plans to reformulate the older product. The sales volume of some products was too small to cover the cost of reformulation. Also, only one substitute active ingredient was available for weight control drug products. Hence, FDA estimates that only about 100 products were reformulated.

The cost to reformulate a product varies greatly depending on the nature of the change in formulation, the product, the process, and the size of the firm. To reformulate, manufacturers also have to redo validation (product, process, new supplier), conduct stability tests, and change master production records. FDA estimates that the full cost of reformulation ranged from $100,000 to $500,000 per product. Assuming that 100 products were reformulated implies

a total estimated one-time reformulation cost of from $10 million to $50 million.

Manufacturers that reformulated would also have incurred costs to relabel their products. They would have had to revise the active (and for some the inactive) ingredient list and may have had to make other labeling changes if they removed the phenylpropanolamine from a combination product and did not replace it with another ingredient. FDA believes that relabeling costs of the type required by this proposed rule generally averaged about $3,000 to $4,000 per stockkeeping unit (SKU) (individual products, packages, and sizes). Assuming 350 OTC SKUs in the marketplace were relabeled, the total one-time costs of relabeling would have ranged from $1.05 to $1.4 million.

Using 2000 as the baseline year for affected products, the total estimated one-time costs for reformulation and labeling range from $11 million to $51 million. Annualized over 20 years yields annual costs of $0.7 - $3.4 million (at 3 percent) and $1.0 - $4.8 million (at 7 percent).

b. *Distributional issues and impact on industry.* Other costs incurred by the industry include costs associated with the recall and destruction of inventory and the loss of product sales. FDA does not have reliable information to estimate either the incremental impacts of recalling and destroying product or to distinguish the market response to the results of the Yale study from FDAs announcement and request for voluntary withdrawal . Moreover, industry costs would be offset substantially by countervailing events including avoided lawsuits associated with continued marketing of products containing phenylpropanolamine and possibly reduced insurance costs. The value of lost profit due to lost product sales would generally be offset as firms gain sales

by distributing substitute products. These gains and losses represent transfers within the industry and are not a social cost.

Reports of withdrawal related expenses from trade press and some 10–K filings with the Securities and Exchange Commission include other costs not attributable to costs of this regulation, such as set-asides for potential litigation. Because of this, we cannot use these reports as a basis for estimating regulatory costs. These reports, however, provide anecdotal information about the magnitude of the impact of the voluntary actions on specific firms. One of the hardest hit large multinational firms explained that the Company immediately ceased global production and shipments of any products containing phenylpropanolamine and voluntarily withdrew any such products from customer warehouses and retail store shelves. As a result, the Company recorded a special charge of $80,000,000 to provide primarily for product returns and the write-off of inventory" (Ref. 9). Another heavily impacted large firm claimed that withdrawal would cost between $51 and $68 million (Ref. 10). Similarly, a large private-label manufacturer reportedly took a $24 million charge against earnings (Ref. 11). These last two figures likely included costs of product reformulation as well as lost inventory value and sales revenues. These accounts represent projections and are estimates for financial reporting requirements but do not accurately reflect actual costs used for regulatory impact analyses.

FDA believes that the lost sales estimates may be overstated, as alternative cough-cold drug products were widely available. Most manufactures quickly offered alternative products and received offsetting increases in sales revenues. OMB guidelines for economic analysis state that, "[t]he preferred measure of

cost is the 'opportunity cost of the resources used or the benefits forgone as a result of the regulatory action" (Ref. 7).

The costs of reformulation, recalls, and lost inventories are clearly "opportunity costs," but the company sales revenues lost from recalled phenylpropanolamine-containing cough-cold drug products were likely matched by increased sales of other phenylpropanolamine-free products, frequently manufactured by the same or competing drug companies. These distributional effects are important to individual firms, but are not considered "opportunity costs."

c. *Summary of costs.* The regulatory costs of the proposed rule would include: (1) The one-time costs to reformulate and relabel affected products, (2) lost inventory, and (3) the cost of recalls. We estimate one-time costs of $11 million to $51 million for reformulation and labeling. Annualized over 20 years yields annual costs of $0.7 - $3.4 million (at 3 percent) and $1.0 - $4.8 million (at 7 percent). We lack sufficient information to estimate the value of lost inventories or the costs of recall. The uncertainty associated with the costs presented in financial reports and the inability to adjust for transfers makes it impossible to use these data to estimate the potential incremental regulatory impact of this proposed rule.

C. Benefits of Regulation

The benefit of removing phenylpropanolamine-containing products from the market was the reduction in the number of hemorrhagic strokes that would otherwise occur each year. Because phenylpropanolamine-containing OTC drug products have already been removed from the market, most of the expected health benefits are attributable to these past voluntary product withdrawals, rather than to FDA's future regulatory action. FDA has estimated

that phenylpropanolamine causes 200 to 500 hemorrhagic strokes per year in people 18 to 49 years old (Ref. 5).

Assigning a monetary value to the prevention of strokes is problematic and there is no consensus on how it should be calculated. Taylor (Ref. 12) used a lifetime cost model to estimate the cost, by type of stroke. The model accounts for direct medical costs and indirect costs, such as earnings and premature mortality and morbidity. Updating this estimate to 2003 dollars (Ref. 13) and weighting it for the occurrence rate of subarachnoid and intracerebral hemorrhage (60 percent and 40 percent, respectively) (Ref. 14) results in an estimated figure of about $304,719 for the lifetime cost of stroke per person. With these values, the monetized benefit of preventing from 200 to 500 strokes per year by removing all phenylpropanolamine-containing OTC drug products from the market ranges from $60.9 million to $152.4 million per year. When groups less than 18 and over 49 years old (the ages of the subjects in the Yale Hemorrhagic Stroke Project) are included, the total yearly benefits will be higher.

Another method of calculating benefits is to value the statistical-lives saved due to the removal of drug products containing phenylpropanolamine. Assuming a mortality rate from phenylpropanolamine-caused strokes of about 25 percent, an estimated 50 to 125 lives saved per year in people 18 to 49 years old would be attributed to the removal of products containing phenylpropanolamine. The value of a statistical-life has been estimated to range from $1.6 million to $8.5 million 1986–dollars (Ref. 15). Using a rough midpoint value of $5 million per statistical-life, the estimated benefit of averting these stroke-induced fatalities ranges from $250 million to $625 million per year. Again, FDA is not asserting that this proposed rule will

generate such benefits, because the benefit-producing activities have already occurred. Nevertheless, to the extent that some phenylpropanolamine-containing OTC drug products might remain available or might return to the market, some fraction of these benefits would be attributable to the issuance of this proposed rule.

D. Small Business Impacts

A drug manufacturer is defined as small by the Small Business Administration if it employs fewer than 750 people. Approximately 70 percent of all OTC drug manufacturers meet the definition of a small entity, and FDA believes that the same rate applies to manufacturers of phenylpropanolamine-containing OTC drug products. Hence, 70 of the 100 manufacturers were classified as small. The cost to distributors and repackers was not significant because the manufacturers of the products bore the brunt of the recall costs, product destruction, and usually were responsible for designing new labels. As explained in this section, to the extent that there are still phenylpropanolamine-containing OTC drug products being marketed, the impact on a manufacturer can vary greatly depending on the number and type of phenylpropanolamine-containing products it produces, the availability of substitute ingredients, and the number of SKUs that will require reformulation and/or relabeling. For example, a small branded product manufacturer may have to reformulate three products and relabel nine SKUs for a total one-time reformulation and relabeling cost ranging from $327,000 (3 products x $100,000 reformulation + 9 SKUs x $3,000 label) to $1.536 million (3 products x $500,000 reformulation + 9 SKUs x $4,000 label). Because there is only one substitute available for OTC weight control drug products, the manufacturer would have to cease production of its existing product and the impact to the

firm would be lost sales. The lost sales could be partially offset by sales of a substitute product, if marketed. The cost of the voluntary product recall would also vary by firm and again depend on the number and quantity of products that needed to be recalled and destroyed.

Because these products must be manufactured in compliance with the pharmaceutical current good manufacturing practices (21 CFR parts 210 and 211), all firms would have the necessary skills and personnel to perform these tasks either in-house or by contractual arrangement. No additional professional skills are needed. In addition, there are no other Federal rules that duplicate, overlap, or conflict with the proposed rule.

FDA considered but rejected alternatives such as leaving products containing this ingredient on the OTC market, or not publicly announcing our intent to reclassify phenylpropanolamine as a Category II ingredient. These alternatives were unacceptable because the health risk posed by products containing phenylpropanolmine was greater than the benefits the products provided, especially given the number of substitute OTC drug products available that did not pose such risks. To have further delayed the removal of OTC phenylpropanolamine drug products from the market would have left consumers exposed to an unacceptable level of risk.

Because the cost of removal and reformulation of phenylpropanolamine containing OTC drug products has already been incurred when the products were voluntarily recalled, and FDA has chosen to use the present as a baseline for its analysis, FDA tentatively concludes that this proposed rule will not have a significant impact on a substantial number of small entities.

V. Paperwork Reduction Act of 1995

FDA tentatively concludes that there are no paperwork requirements in this document under the Paperwork Reduction Act of 1995 (44 U.S.C. 3501 *et seq.*).

VI. Environmental Impact

The agency has determined under 21 CFR 25.31(a) that this action is of a type that does not individually or cumulatively have a significant effect on the human environment. Therefore, neither an environmental assessment nor an environmental impact statement is required.

VII. Federalism

FDA has analyzed this proposed rule in accordance with the principles set forth in Executive Order 13132. FDA has determined that the proposed rule does not contain policies that have substantial direct effects on the States, on the relationship between the National Government and the States, or on the distribution of power and responsibilities among the various levels of government. Accordingly, the agency tentatively concludes that the proposed rule does not contain policies that have federalism implications as defined in the Executive order and, consequently, a federalism summary impact statement has not been prepared.

VIII. Request for Comments

Three copies of all written comments are to be submitted. Individuals submitting written comments or anyone submitting electronic comments may submit one copy. Comments are to be identified with the docket numbers found in brackets in the heading of this document and may be accompanied by a supporting memorandum or brief. Received comments may be seen in the Division of Dockets Management between 9 a.m. and 4 p.m., Monday through Friday.

IX. Time for Submission of New Data

The OTC drug review procedures (21 CFR 330.10(a)(7)(iii)) provide for a 12-month period after publication of a TFM for any interested person to file new data and information to support a condition excluded from the monograph in the TFM. As discussed in section I of this document, FDA has published proposed and final rules for OTC nasal decongestant and weight control drug products and deferred a decision on the status of phenylpropanolamine so new data on this ingredient could be included in the record before a TFM or notice of proposed rulemaking was published. Manufacturers have been aware of this deferral for a number of years and have waited for the results of the study described in section II of this document to resolve the monograph status of phenylpropanolamine. It has taken many years for the phenylpropanolamine study to be completed, and the results indicate a major safety concern about this ingredient. FDA does not believe that any additional significant new safety data and information will be presented in the next 12 months. Because of the need to address and finalize FDA action on the existing safety concerns, and because there has already been public consideration of the issues before an FDA advisory committee, the comment period and the time for submission of new data is 90 days. FDA considers it an important public health concern to complete its classification of phenylpropanolamine preparations in OTC drug products as quickly as possible.

X. Proposed Effective Date

FDA is proposing that any final rule that may issue based on this proposal become effective 30 days after its date of publication in the **Federal Register**.

XI. References

The following references are on display in the Division of Dockets Management (see **ADDRESSES**) and may be seen by interested persons between

9 a.m. and 4 p.m., Monday through Friday. (FDA has verified the Web site address, but we are not responsible for subsequent changes to the Web site after this document publishes in the **Federal Register**.)

1. Comment No. LET86, Docket No. 1981N–0022 (formerly Docket No. 81N–0022).

2. Horwitz et al., "Phenylpropanolamine & Risk of Hemorrhagic Stroke: Final Report of The Hemorrhagic Stroke Project," May 10, 2000 in Comment No. C230, Docket No. 1976N–0052N (formerly Docket No. 76N–052N) and Comment No. RPT14, Docket No. 1981N–0022 (formerly Docket No. 81N–0022).

3. Phenylpropanolamine case reports from 1991 to 2000 on file in Docket Nos. 1976N–0052N (formerly 76N–052N) and 1981N–0022 (formerly 81N–0022).

4. Consumer Healthcare Products Association (CHPA), "Comments on the Hemmorhagic Stroke Project Report," May 24, 2000, in Comment No. C231, Docket No. 1976N–0052N (formerly Docket No. 76N–052N) and Comment No. C113, Docket No. 1981N–0022 (formerly Docket No. 81N–0022).

5. Food and Drug Administration, Transcript of Nonprescription Drugs Advisory Committee meeting, October 19, 2000, in Docket Nos. 1976N–0052N, (formerly 76N–052N) and 1981N–0022 (formerly 81N–0022).

6. Food and Drug Administration, Public Health Advisory, "Safety of Phenylpropanolamine," November 6, 2000, Comment No. M1 in Docket No. 1976N–0052N (formerly 76N–052N) and Comment No. M7 in Docket No. 1981N–0022 (formerly 81N–0022).

7. Office of Management and Budget, "Guidelines to Standardized Measures of Costs and Benefits and the Format of Accounting Statements,"

M0008, March 22, 2000, downloaded from *http://www.whitehouse.gov/omb/memoranda/index.html*, accessed June, 13, 2001.

8. Jarvis, Lisa, "PPA Ban Is a Serious Threat to OTC Diet Aids," Chemical Market Reporter, November 20, 2000.

9. U.S. Security and Exchange Commission, Form 10-K, Voluntary Market Withdrawals, fiscal year ended December 31, 2000, American Home Products Corp., in Docket Nos. 1976N–0052N (formerly Docket No. 1976N–052N) and 1981N–0022.

10. F-D-C Reports-"The Tan Sheet," "Dexatrim Natural Fattens Chattem's First Quarter; Extensions Planned," vol. 9, no. 14, April 2, 2001.

11. F-D-C Reports-"The Tan Sheet," "AHP Dimetapp, Robitussin PPA Withdrawals Lead To $80 Mil. Charge In 2000," vol. 9, no. 5, January 29, 2001.

12. Taylor, Thomas N., "The Medical Economics of Stroke," Drugs, supp. 3:51–58, 1997.

13. U.S. Census Bureau, No. 768, Consumer Price Index by Major Group., downloaded from *http://www.census.gov/statab/freq/00s0768.txt*, accessed June 12, 2001. U.S. Bureau of Labor Statistics, accessed July 23, 2004. Updated 1999 data to 2003 (18.56 percent increase in medical care CPI).

14. Kernan, Walter N. et al., "Phenylpropanolamine and the Risk of Hemorrhagic Stroke," *The New England Journal of Medicine*, 343: 1826–1832, 2000.

15. Fisher, A., L., G. Chestnut, and D. M. Violette, "The Value of Reducing Tisks of Death: a Note on New Evidence," *Journal of Policy Analysis and Management*, 8: 88–100, 1989.

List of Subjects

21 CFR Part 310

Administrative practice and procedure, Drugs, Labeling, Medical devices, Reporting and recordkeeping requirements.

21 CFR Part 341

Labeling, Over-the-counter drugs.

21 CFR Part 357

Labeling, Over-the-counter drugs, Reporting and recordkeeping requirements.

Therefore, under the Federal Food, Drug, and Cosmetic Act and under authority delegated to the Commissioner of Food and Drugs, it is proposed that 21 CFR parts 310, 341 (as proposed in the **Federal Register** of September 9, 1976 (41 FR 38312)), and 357 (as proposed in the **Federal Register** of February 26, 1982 (47 FR 8466)) be amended as follows:

PART 310–NEW DRUGS

1. The authority citation for 21 CFR part 310 continues to read as follows:

Authority: 21 U.S.C. 321, 331, 351, 352, 353, 355, 360b–360f, 360j, 361(a), 371, 374, 375, 379e; 42 U.S.C. 216, 241, 242(a), 262, 263b–263n.

2. Section 310.545 is amended by redesignating the text of paragraph (a)(20) as paragraph (a)(20)(i) and by adding paragraph (a)(20)(i) heading, by adding paragraphs (a)(6)(ii)(D), (a)(20)(ii), and (d)(35), and by revising paragraph (d)(2) to read as follows:

§ 310.545 Drug products containing certain active ingredients offered over-the-counter (OTC) for certain uses.

(a) * * *

(6) * * *

(ii) * * *

(D) Approved as of [date 30 days after date of publication in the **Federal Register**]. Any phenylpropanolamine ingredient.

* * * * *

(a) * * *

(20) * * *

(i) Approved as of February 8, 1991. * * *

(ii) Approved as of [date 30 days after date of publication in the **Federal Register**]. Any phenylpropanolamine ingredient.

* * * * *

(d) * * *

(2) February 10, 1992, for products subject to paragraph (a)(20)(i) of this section.

* * * * *

(35) [Date 30 days after date of publication in the **Federal Register**], for products subject to paragraphs (a)(6)(ii)(D) and (a)(20)(ii) of this section.

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

3. The authority citation for 21 CFR part 341 continues to read as follows:

Authority: 21 U.S.C. 321, 351, 352, 353, 355, 360, 371.

§ 341.20 [Amended]

4. Section 341.20 of the proposed rule published at 41 FR 38312 is amended by removing paragraph (e) and redesignating paragraphs (f), (g), and (h) as paragraphs (e), (f), and (g), respectively.

SR per Karen at OFR

PART 357–MISCELLANEOUS INTERNAL DRUG PRODUCTS FOR OVER-THE-COUNTER HUMAN USE

5. The authority citation for 21 CFR part 357 continues to read as follows:

Authority: 21 U.S.C. 321, 351, 352, 353, 355, 360, 371.

§ 357.510 [Amended]

6. Section 357.510 of the proposed rule published at 47 FR 8466 is amended by removing and reserving paragraph (b). SR

§ 357.520 [Removed]

7. Section 357.520 of the proposed rule published at 47 FR 8466 is removed. SR

§ 357.550 [Amended]

8. Section 357.550 of the proposed rule published at 47 FR 8466 is amended by removing and reserving paragraphs (c)(2) and (d)(2). SR.

§ 357.555 [Removed]

9. Section 357.555 of the proposed rule published at 47 FR 8466 is removed. SK.

Dated: 12/5/05

December 5, 2005.

Jeffrey Shuren,
Assistant Commissioner for Policy.

CERTIFIED TO BE A TRUE COPY OF THE ORIGINAL

[FR Doc. 05–????? Filed ??–??–05; 8:45 am]

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