TAB 1

ISSUE: THE SAFETY OF PHENYLPROPANOLAMINE HYDROCHLORIDE (PPA) USED IN OTC WEIGHT CONTROL AND NASAL DECONGESTANT DRUG PRODUCTS

Background

In the FEDERAL REGISTER of February 26, 1982 (47 FR 8466), FDA published, under § 330.10(a)(6) (21 CFR 330.10(a)(6)), an advance notice of proposed rulemaking (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 (the Panel), which was the advisory review panel responsible for evaluating data on the active ingredients in this drug class.

In the ANPR (47 FR 8466), the Panel classified 113 OTC weight control drug product ingredients. Of these, two (benzocaine and phenylpropanolamine hydrochloride) were placed in Category I (safe and effective); 100 were Category II (not safe and effective); and 11 were Category III (more data needed).

In the FEDERAL REGISTER of October 30, 1990 (55 FR 45788), FDA published a notice of proposed rulemaking (proposed rule) stating that the 111 ingredients classified in Category II and III by the Panel are not generally recognized as safe and effective and that OTC drug products containing these ingredients as active ingredients for weight control are misbranded. FDA did not receive any substantive comments or new data or information

in opposition to the Panel's proposed nonmonograph status for these ingredients and the agency's notice of proposed rulemaking.

In the FEDERAL REGISTER of August 8, 1991 (56 FR 37792), FDA published a final rule stating that the presence of any of these 111 active ingredients in an OTC weight control drug product would result in that drug product not being generally recognized as safe and effective and being misbranded. The final rule became effective on February 10, 1992.

In the 1982 weight control ANPR, the Panel recommended that phenylpropanolamine be classified in Category I in an immediate-release dose of 25 to 50 milligrams (mg) and a timed-release dose of up to 150 mg phenylpropanolamine, with the total daily dose not to exceed 150 mg in either case (47 FR 8466 at 8474). Reports, which became available after the Panel completed its evaluation, indicated that higher doses of phenylpropanolamine than were currently marketed caused elevation of blood pressure (47 FR 8466 to 8469). The agency discussed these reports in the preamble and specifically requested comments and information on the extent to which phenylpropanolamine induces hypertension in normotensive persons or aggravates pre-existing hypertension. The agency also requested information on the dissolution rates of timed-release weight control drug products containing

phenylpropanolamine to determine if a safety problem is posed by these products that would require action before a final monograph is issued.

Based on the reports of phenylpropanolamine's blood pressure effects, the agency concluded that it was not necessary to remove from the market products containing phenylpropanolamine dosage levels that had an OTC marketing history. However, until the safety concerns were resolved, the agency would prohibit any increase in OTC phenylpropanolamine weight control dosages above those in use on December 4, 1975 (47 FR 8466 at 8468). Thus, OTC weight control drug products were limited to an immediate-release dose of 25 to 37.5 mg and a timed-release dose of up to 75 mg phenylpropanolamine, with the total daily dose not to exceed 75 mg in either case. Similarly, the agency retained the phenylpropanolamine dosage levels that had a marketing history of use in OTC nasal decongestant drug products (for adults, 25 mg every 4 hours or 50 mg every 8 hours, not to exceed 150 mg in 24 hours) because these products are used around the clock.

After preliminary evaluation of the submitted information, FDA concluded that phenylpropanolamine produces hemodynamic effects (raises blood pressure) and that the data were inadequate to respond to the agency's concerns regarding the extent to which

phenylpropanolamine induces or aggravates hypertension. The data regarding the pharmacokinetics of the timed-release formulations were also found to be inadequate.

FDA informed the industry that data were required from epidemiological studies of a case-control or cohort design that would (1) examine the role phenylpropanolamine plays as a potential risk factor for adverse events such as stroke or seizure and other serious adverse reactions that have been reported following ingestion of this drug and (2) identify additional suspected risk factors (e.g., age, hypertension, concomitant drug use, or disease conditions) in conjunction with the use of phenylpropanolamine.

As the agency was completing its review of the data and information submitted to the rulemaking on OTC weight control drug products, the House Small Business Subcommittee on Regulation, Business Opportunities, and Energy held a hearing on September 24, 1990, to examine adolescent dieting behavior, diet pills containing phenylpropanolamine, and Federal research efforts on obesity. Witnesses at the hearing expressed concern about the previously narrow focus of FDA's consideration of the efficacy and safety of phenylpropanolamine. Some scientific experts called for a wider consideration of efficacy than the

narrow scope, short-term clinical studies that constituted the prior focus of FDA scrutiny.

In a notice published in the FEDERAL REGISTER of April 1, 1991 (56 FR 13295), the agency announced that an open public meeting would be held on May 9, 1991, to discuss the safety and effectiveness of phenylpropanolamine for OTC weight control use. Specific topics discussed at the meeting included phenylpropanolamine's effects on measured blood pressure, safety concerns relating to central nervous system adverse effects (especially stroke and intracranial hemorrhage), and the implications of possible misuse of phenylpropanolamine as an OTC weight control product.

Because of concerns that FDA might remove OTC phenypropanolamine weight control drug products from the market, the Nonprescription Drug Manufacturers Association (NDMA) proposed in a meeting on November 9, 1992, a large-scale epidemiologic case-control study of phenylpropanolamine and hemorrhagic stroke. After review and modification of the study protocol by FDA, the study began in September, 1994. The study was completed in June, 1999.

As FDA was evaluating the safety study protocol, the agency issued a letter to NDMA dated March 9, 1993, outlining its

concerns regarding the safety of phenylpropanolamine. In that letter, FDA informed industry that the agency intended to classify phenylpropanolamine in Category III (insufficient data) for safety in the proposed rules for OTC weight control and nasal decongestant drug products. The principal concern is the possibility that phenylpropanolamine used in OTC drug products is associated with an increased risk of hemorrhagic stroke. That possibility was raised by a relatively small number of spontaneous reports of intracranial bleeding associated with the use of OTC weight control drug products. However, without a reasonable estimate of the extent of under-reporting, the agency has found it impossible to determine whether the reported instances of intracranial bleeding are more than the expected background rate or these events in young women 15 to 44 years of age.

Because of the difficulties of the analysis, FDA asked three epidemiologists from outside the agency to review its assessment of the stroke data. Although the epidemiologists agreed that FDA's analysis was reasonable based on the available data, they also believed that interpretation of the data depends critically on the estimated reporting rate of phenylpropanolamine-associated adverse drug reactions in the OTC setting and that the reporting

rate is unknown. Because this rate is unknown, they agreed that the database did not support a conclusion that phenylpropanolamine is associated with an increased rate of strokes. However, they also agreed that the available data could not rule out the possibility of an increase in the stroke rate.

The purpose of the NDAC meeting is to determine (1) whether the results of this study provide evidence that phenylpropanolamine used in OTC nasal decongestant and weight control drug products is associated with an increased risk of stroke and (2) NDAC's recommendations concerning the OTC status of this ingredient.