

Food and Drug Administration
Rockville MD 20857

June 21, 2001

Laura M. Nagel
Deputy Assistant Administrator
Office of Diversion Control
Drug Enforcement Administration
United States Department of Justice
Washington, D.C. 20527

Dear Ms. Nagel:

This is in response to your letter of May 23, 2001, requesting an opinion on two issues: (1) whether ephedrine hydrochloride (HCl), pseudoephedrine HCl, and phenylpropanolamine HCl are considered drugs under the Federal Food, Drug, and Cosmetic Act (FFDCA) when they are intended for use as ingredients in a dietary supplement; and (2) whether products containing phenylpropanolamine are safe for human consumption in light of the recent Food and Drug Administration (FDA) advisory on phenylpropanolamine. Your letter states that the Drug Enforcement Administration (DEA) has recently received requests for the importation of large quantities of ephedrine HCl, pseudoephedrine HCl, and phenylpropanolamine HCl for use in the manufacture of products to be marketed as dietary supplements.

Factual Background

Ephedrine alkaloids--(-)-ephedrine, (+)-pseudoephedrine, (-)-norephedrine ((-)-phenylpropanolamine), (+)-norpseudoephedrine, (-)-N-methylephedrine, and (+)-N-methylpseudoephedrine--are amphetamine-like compounds that stimulate the cardiovascular and nervous systems of the body. Ephedrine HCl, pseudoephedrine HCl, and phenylpropanolamine HCl are synthetically produced ephedrine alkaloids in salt form. Ephedrine alkaloids are also found in nature as constituents of several botanicals of the *Ephedra* and *Pinella* genera. Botanical ephedrine alkaloids exist in plants in free-base form, not salt form.

Legal Analysis

Under the FFDCA, the definition of "drug" includes, among other things, "articles (other than food) intended to affect the structure or any function of the body of man or other animals." 21 U.S.C. § 321(g)(1)(C). The definition of "dietary supplement" is set forth at 21 U.S.C. § 321(ff). Among other requirements, a dietary supplement must be intended to supplement the diet and must contain one or more of the following "dietary ingredients":

- (A) a vitamin;
- (B) a mineral;
- (C) an herb or other botanical;
- (D) an amino acid;
- (E) a dietary substance for use by man to supplement the diet by increasing the total dietary intake;
- (F) a concentrate, metabolite, constituent, extract, or combination of any ingredient described in clause (A), (B), (C), (D), or (E).

21 U.S.C. § 321(ff)(1)(A)-(F).

Under certain conditions, dietary supplements may bear claims about the effects of a dietary ingredient on the structure or function of the body without being considered drugs. See 21 U.S.C. §§ 321(g)(1), 343(r)(6). Importers and manufacturers who wish to take advantage of this partial exception from the drug definition may argue that ephedrine HCl, pseudoephedrine HCl, and phenylpropanolamine HCl are dietary ingredients when they are intended for use in dietary supplements. FDA has considered the regulatory status of these compounds and has concluded that they are not "dietary ingredients" as defined in 21 U.S.C. § 321(ff)(1).

Ephedrine HCl, pseudoephedrine HCl, and phenylpropanolamine HCl are not vitamins, minerals, or amino acids under § 321(ff)(1)(A), (B), or (D). Because they are not plants or physical parts of plants (e.g., a leaf, stem, or root), they are not herbs or other botanicals under § 321(ff)(1)(C). Nor does FDA believe that these chemicals are "dietary substance[s] for use by man to supplement the diet by increasing the total dietary intake" under § 321(ff)(1)(E). The term "dietary substance" is not defined in the FFDCA; accordingly, FDA interprets it in accordance with its common, usual meaning. *Webster's II New Riverside University Dictionary* defines "dietary" as "of or pertaining to the diet" and "diet" as "an organism's usual food or drink." Accordingly, a "dietary substance" means a

substance that is commonly used as human food or drink. The statutory language "for use by man to supplement the diet by increasing the total dietary intake" supports this interpretation; one cannot increase the total dietary intake of something that is not customarily part of the diet in the first place. Ephedrine HCl, pseudoephedrine HCl, and phenylpropanolamine HCl are not commonly used as food or drink by humans.

Moreover, ephedrine HCl, pseudoephedrine HCl, and phenylpropanolamine HCl are not dietary ingredients under § 321(ff)(1)(F) because they are not concentrates, metabolites, constituents, extracts, or combinations of any of the other types of dietary ingredients. These synthetic compounds cannot be obtained by concentrating, metabolizing, or combining vitamins, minerals, amino acids, botanicals, or dietary substances. Nor are the three compounds in question constituents or extracts of any other type of dietary ingredient. Although botanical ephedrine alkaloids are constituents of botanicals of the *Ephedra* and *Pinella* genera and may be extracted from them, synthetic ephedrine alkaloids like ephedrine HCl, pseudoephedrine HCl, and phenylpropanolamine HCl are not plant-derived and therefore are not constituents or extracts of any botanical source. Some forms of synthetic ephedrine alkaloids may be chemically indistinguishable from botanical ephedrine alkaloids; however, a substance that has never been physically a part of a whole cannot be a constituent or extract of that whole.

Further, ephedrine HCl, pseudoephedrine HCl, and phenylpropanolamine HCl are not constituents of a dietary substance because they are not inherent components of anything commonly used as human food or drink. Likewise, they are not extracts of any dietary substance. Therefore, ephedrine HCl, pseudoephedrine HCl, and phenylpropanolamine HCl are not dietary ingredients under 21 U.S.C. § 321(ff)(1).

Ephedrine HCl, pseudoephedrine HCl, and phenylpropanolamine HCl do, however, meet the definition of a drug under 21 U.S.C. § 321(g)(1)(C). They are not food and are unquestionably intended to affect the structure or function of the human body by stimulating the cardiovascular and nervous systems. Therefore, they are drugs and may be regulated as such.

Safety of Phenylpropanolamine HCl

You have also asked whether phenylpropanolamine HCl is safe for human consumption. On November 6, 2000, FDA issued a public health advisory recommending that consumers not use any drug products containing phenylpropanolamine HCl because of the concern that phenylpropanolamine HCl increases the risk of hemorrhagic stroke. The agency has requested that all drug companies discontinue marketing products containing phenylpropanolamine HCl and is taking steps to remove phenylpropanolamine HCl as an ingredient in OTC and prescription drug products.

I hope that this information is helpful.

Sincerely,

A handwritten signature in black ink, appearing to read "Dennis E. Baker". The signature is fluid and cursive, with a large initial "D" and a long horizontal stroke extending to the right.

Dennis E. Baker
Associate Commissioner for
Regulatory Affairs