[Docket No. 82N-0266]

New Drug Status of OTC Combination Drug Products Containing Caffeine, Phenylpropanolamine, and Ephedrine

AGENCY: Food and Drug Administration.

ACTION: Notice.

SUMMARY: The Food and Drug Administration (FDA) announces that it

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has determined that combination drug products consisting of caffein, phenylpropanolamine, and ephedrine are new drugs and as such are required to be the subject of an approved new drug application (NDA). FDA has concluded that this combination, available over-the-counter (OTC) and typically labeled for use as a nasal decongestant, bronchodilator, and stimulant, is not included in the OTC Drug Review. FDA further states its conclusion that these products present a potential hazard to health. The agency revokes any prior advisory opinion that would preclude enforcement against these products.

EFFECTIVE DATE: August 13, 1982.

FOR FURTHER INFORMATION CONTACT: Eileen R. Hodkinson, National Center for Drugs and Biologics (HFD-30), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857; 301-443-6490.

SUPPLEMENTARY INFORMATION: Combination drug products consisting of the triple combination of caffeine, phenylpropanolamine, and ephedrine and/or their salts are currently available over-the-counter (OTC) and are labeled for uses as a nasal decongestant, bronchodilator, and stimulant and for use as a diet aid/stimulant. The agency has determined that these drug products are new drugs as defined under section 201(p) of the Federal Food, Drug, and Cosmetic Act (the Act) (21 U.S.C. 321(p)) in that they are not generally recognized, among experts qualified by scientific training and experience to evaluate the safety and effectiveness of drugs, as safe and effective for use under the conditions prescribed, recommended, or suggested in their labeling, and they have not been used for a material time or to a material extent.

As a general rule, FDA has deferred new drug enforcement actions with respect to products included in the ongoing OTC Drug Review. In the agency's view, however, this triple-combination product is not the kind of product that is, or was ever intended to be, included in the OTC Drug Review. No evidence on the safety or effectiveness of the triple combination was submitted to the Review. In addition to having no known medical rationale, the triple combination has a highly suspect marketing history, suggesting that it is frequently used to mimic, and capitalize on the market for, controlled substances.

Although individual active ingredients of this triple combination, at certain levels and for certain indications, alone and in some combinations are being reviewed in the OTC Drug Review, the agency has concluded that the triple combination is not included in the Review. Any prior statements by FDA emloyees suggesting that the triple combination is included in the OTC Drug Review are incorrect and are hereby revoked.

The agency also believes that this triple combination presents a potential health hazard. The combination of caffeine, phenylpropanolamine, and ephedrine has been marketed and promoted as a product capable of producing effects similar to those produced by controlled substances, and has been widely misused and abused. Even when taken as indicated in its labeling, however, this combination drug product is known to cause excess central nervous system stimulation that could have adverse physiological consequences. Further, the combination of these three ingredients is irrational and without medical justification; the concomitant symptoms of nasal congestion, asthma, and the need for stimulation at the same time does not occur in any significant patient population. Nor has ephedrine been shown effective as a diet aid. Thus, because of this potential health hazard, even if the combination were under review as part of the OTC Drug Review, enforcement action against the triple combination as a new drug would be appropriate.

Therefore, because products containing the triple combination of ingredients, i.e., caffeine, phenylpropanolamine, and ephedrine and/or their salts, are new drugs and no approval of an application filed pursuant to section 505(b) of the act is effective for such drugs, nor is a notice of claimed investigational exemption pursuant to section 505(i) of the act and 21 CFR 312.1 on file, shipment of these products in interstate commerce violates section 301(d) of the act (21 U.S.C. 331(d)). Further, under section 502(f)(1) of the act (21 U.S.C. 352(f)(1)), these drugs are misbranded in that their labeling fails to bear adequate directions for use and they are not exempt from such requirements under 21 CFR 201.115 because they are unapproved new drugs. Shipment of these drugs in interstate commerce and their manufacture from components received in interstate commerce violate section 301 (a) and (k) of the act, respectively. Persons engaging or participating in or causing the manufacture or shipment of these drugs are subject to regulatory action, and the drugs themselves are subject to seizure under section 304 of the act (21 U.S.C. 334).

As explained above, FDA has concluded that these products were never intended to be included in the OTC Drug Review and that, even if they were included, enforcement actions could be taken against these products consistent with FDA's Compliance Policy Guide because the drugs present a potential health hazard. In any case, this document, as an official advisory opinion by FDA, removes any potential restraint on enforcement actions brought with respect to these drugs. Such a restraint could be argued to exist because the agency's Compliance Policy Guide is, in some circumstances, an advisory opinion of the agency that must be followed until amended or revoked (21 CFR 10.85 (d)(3) and (e)). An advisory opinion may, however, be amended or revoked at any time after it is issued, and notice of amendment of revocation may be given in the Federal Register. This is such a notice. Any statement by FDA, in the Compliance Policy Guide or otherwise, that suggests in any way that enforcement will not be taken against the products referred to in this notice is hereby revoked to the extent that that statement applies to such products. In addition, the Commissioner of Food and Drugs has determined that substantial public interest considerations preclude continued acceptance by FDA of any action undertaken or completed in alleged conformity with what anyone may believe to have been a prior advisory opinion that these products could be legally marketed, *see* 21 CFR 10.85(h). Because there is no legitimate use for these products, no transition period for use of the products is applicable, *id.*

The agency has considered whether there is any need to undertake notice and comment rulemaking in order to state in the Federal Register its position on these drugs. It has concluded that no such requirement exists. This statement, even if taken as a revocation of valid prior advisory opinions, is in accordance with FDA's regulations which do not require notice and comment rulemaking for publication of such revocation. In addition, this statement of the agency policy with respect to these drugs is not a substantive rule because it does not have, in it and of itself, the force and effect of law. *Cf. Burroughs Wellcome Co.* v. *Schweiker*, 649 F. 2d 221, 225 (4th Cir. 1981). This announcement is not a "declaration" that the drug is a new drug made after appropriate administrative proceedings. Rather, it is a statement of FDA's position. The government is prepared to present proof to support the agency's conclusion that

these products are new drugs in the course of any action that may be brought to enforce the law with respect these products. *Cf. United States* v. *Article of Drug * * * X-Otag Plus Tablets*, 602 F. 2d 1387, 1390–91 (10th Cir. 1979).

Dated: August 10, 1982.

Arthur Hull Hayes, Jr.,

Commissioner of Food and Drugs.

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