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# Guidance for Industry

*The FDA published Good Guidance Practices in February 1997.  
This guidance was developed and issued prior to that date.*

Additional copies are available from:  
Office of Training and Communications  
Division of Communications Management  
Drug Information Branch, HFD-210  
5600 Fishers Lane  
Rockville, MD 20857

(Tel) 301-827-4573  
(Internet) <http://www.fda.gov/cder/guidance/index.htm>

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES, FOOD AND DRUG ADMINISTRATION

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[4110-03-M]

Food and Drug Administration

[Docket No. 78D-0322]

**OTC COMBINATION DRUG PRODUCTS****Availability of Guideline**

AGENCY: Food and Drug Administration.

ACTION: Notice.

**SUMMARY:** This document announces the availability of a guideline that states in detail the agency policy for combining two or more safe and effective over-the-counter (OTC) active drug ingredients. The agency will use this guideline, in addition to the existing regulatory requirements for OTC combination drugs, in evaluating the safety and effectiveness of all OTC combination drug products.

**ADDRESS:** Written comments to the Hearing Clerk (HFA-305), Food and Drug Administration, Rm. 4-65, 5600 Fishers Lane, Rockville, MD 20857.

**FOR FURTHER INFORMATION CONTACT:**

William E. Gilbertson, Bureau of Drugs (HFD-510), Food and Drug Administration, Department of Health, Education, and Welfare, 5600 Fishers Lane, Rockville, MD 20857, 301-443-4960.

**SUPPLEMENTARY INFORMATION:** The regulatory requirements for OTC combination drug products, set forth in § 330.10(a)(4)(iv) (21 CFR 300.10(a)(4)(iv)), are sufficiently general that they allow various interpretations. The OTC drug advisory review panels have been encouraged to exercise their own scientific judgment in developing all aspects of their reports, and different panels have, in fact, variously interpreted the OTC combination regulations. The Commissioner of Food and Drugs is therefore making available a guideline entitled "General Guidelines for OTC Drug Combination Products September 1978" that

specifically sets forth acceptable criteria for combining Category I active ingredients in certain situations that are not covered by the broad regulation. For example, the guidelines explain the Food and Drug Administration's position regarding combinations of ingredients from: different therapeutic categories and which are intended to treat different symptoms; the same therapeutic category but with different mechanisms of action; and the same therapeutic category and with the same mechanism of action. The agency will apply the criteria in the guideline, in addition to the regulatory requirements in § 330.10(a)(4)(iv) in determining the safety and effectiveness of all OTC combination drug products.

The Division of OTC Drug Evaluation (HFD-510), Bureau of Drugs is responsible for maintaining the guideline.

A copy of the guideline is available for public examination between 9 a.m. and 4 p.m., Monday through Friday, in the office of the Hearing Clerk. Requests for single copies of the guideline may be submitted to the office of the Hearing Clerk, identifying the guideline with the Hearing Clerk docket number found in brackets in the heading of this document.

Interested persons may submit written comments on the guideline to the Hearing Clerk (HFA-305), Food and Drug Administration, Rm. 4-65, 5600 Fishers Lane, Rockville, MD 20857 (preferably in four copies, identified with the Hearing Clerk docket number). Such comments will be considered in determining whether amendments or revisions to the guideline are warranted. Received comments will be incorporated into the public file on the guideline and may be seen in the above office between 9 a.m. and 4 p.m., Monday through Friday, except holidays.

Dated: November 21, 1978.

WILLIAM F. RANDOLPH,  
*Acting Associate Commissioner  
for Regulatory Affairs.*

[FR Doc. 78-33215 Filed 11-27-78; 8:45 am]

FOOD AND DRUG ADMINISTRATION

GENERAL GUIDELINES FOR OTC DRUG COMBINATION PRODUCTS

September 1978

In addition to the requirement of the OTC drug regulations (21 CFR 330.10(a)(4)(iv)), the following specific guidelines shall be used for all OTC drug combinations:

- (1) Category I active ingredients from different therapeutic categories may be combined to treat different symptoms concurrently only if each ingredient is present within its established safe and effective dosage range and the combination meets the OTC combination policy in all other respects.
- (2) Category I active ingredients from the same therapeutic category that have different mechanisms of action may be combined to treat the same symptoms or condition if the combination meets the OTC combination policy in all respects and the combination is on a benefit-risk basis, equal to or better than each of the active ingredients used alone at its therapeutic dose. Such combinations may utilize each active ingredient in full therapeutic dosage or sub-therapeutic dosage, as appropriate.
- (3) Category I active ingredients from the same therapeutic category that have the same mechanism of action should not ordinarily be combined unless there is some advantage over the single ingredients in terms of enhanced effectiveness, safety, patient acceptance, or quality of formulation. They may be combined in selected circumstances to treat the same symptoms or conditions if the combination meets the OTC combination policy in all respects, the combination offers some advantage over the active ingredients used alone, and the combination is, on a benefit-risk basis, equal to or better than each of the active ingredients used alone at its therapeutic dose.

- (4) An ingredient claimed to be a pharmacological adjuvant (i.e., to enhance or otherwise alter the effect of another active ingredient) will be considered an active ingredient. Such an ingredient may be included in addition to one or more principal active ingredients only if it meets the combination policy in all respects.
- (5) In some cases an ingredient may be appropriate for use only in a specific combination or data may be available only to support the use of the ingredient in combination but not as a single ingredient. In such cases the ingredient will be placed in Category I for use only in permissible combinations and not as a single ingredient.
- (6) The final OTC monograph will list the combinations permitted for marketing under the monograph. In those cases where the data are sufficient to support a finding by the agency that several ingredients in a therapeutic category can be considered interchangeable for purposes of formulating combinations, the monograph will so state and list those ingredients. This is the preferred approach and will be done whenever supported by the data and the opinion of experts. In those cases where the available information is sufficient to support only specific combinations of active ingredients within a category, these permitted combinations will be listed in the monograph.