

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. 01P-0315]

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Determination That Acetaminophen and Codeine Phosphate Tablets, 500 Milligrams (mg)/15 mg, 500 mg/30 mg, and 500 mg/60 mg, Were Not Withdrawn From Sale for Reasons of Safety or Effectiveness

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

SUMMARY: The Food and Drug Administration (FDA) is announcing its determination that acetaminophen and codeine phosphate tablets, 500 mg/15 mg, 500 mg/30 mg, and 500 mg/60 mg, were not withdrawn from sale for reasons of safety or effectiveness. This determination will allow FDA to approve abbreviated new drug applications (ANDAs) for acetaminophen and codeine phosphate tablets, 500 mg/15 mg, 500 mg/30 mg, and 500 mg/60 mg.

FOR FURTHER INFORMATION CONTACT: Carol E. Drew, Center for Drug Evaluation and Research (HFD-7), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301-594-2041.

SUPPLEMENTARY INFORMATION: In 1984, Congress enacted the Drug Price Competition and Patent Term Restoration Act of 1984 (Public Law 98-417) (the 1984 amendments), which authorized the approval of duplicate versions of drug products approved under an ANDA procedure. ANDA sponsors must, with certain exceptions, show that the drug for which they are seeking approval contains the same active ingredient in the same strength and dosage form as the "listed drug," which is typically a version of the drug that was previously approved under a new drug application (NDA). Sponsors of ANDAs do not have to repeat the extensive clinical testing otherwise necessary

to gain approval of an NDA. The only clinical data required in an ANDA are data to show that the drug that is the subject of the ANDA is bioequivalent to the listed drug.

The 1984 amendments include what is now section 505(j)(7) of the Federal Food, Drug, and Cosmetic Act (the act) (21 U.S.C. 355(j)(7)), which requires FDA to publish a list of all approved drugs. FDA publishes this list as part of the “Approved Drug Products With Therapeutic Equivalence Evaluations,” which is generally known as the “Orange Book.” Under FDA regulations, drugs are withdrawn from the list if the agency withdraws or suspends approval of the drug’s NDA or ANDA for reasons of safety or effectiveness, or if FDA determines that the listed drug was withdrawn from sale for reasons of safety or effectiveness (21 CFR 314.162).

Under § 314.161(a)(1) (21 CFR 314.161(a)(1)), the agency must determine whether a listed drug was withdrawn from sale for reasons of safety or effectiveness before an ANDA that refers to that listed drug may be approved. FDA may not approve an ANDA that does not refer to a listed drug.

There are no NDAs for acetaminophen and codeine phosphate tablets. The initial acetaminophen/codeine combination drug product was accepted as an ANDA based on a **Federal Register** notice finding TRIGESIC with codeine to be effective for the relief of mild to moderate pain. (See 38 FR 3210, February 2, 1973.) FDA made this effectiveness determination under the 1962 amendments to the act, which required a demonstration of the effectiveness of new drugs, including those approved prior to 1962. FDA contracted with the National Academy of Science/ National Research Council to carry out the Drug Efficacy Study assessing the evidence of effectiveness available for new drugs approved prior to 1962. TRIGESIC with codeine contained codeine, acetaminophen, aspirin, and caffeine. The initial ANDA for acetaminophen and codeine tablets was considered to be similar and related to TRIGESIC with codeine tablets, and therefore was accepted as an ANDA.

Roxane Laboratories (Roxane) filed a suitability petition (86P–0161/CP) on April 14, 1986, requesting permission to file ANDAs for three different strengths of acetaminophen and codeine

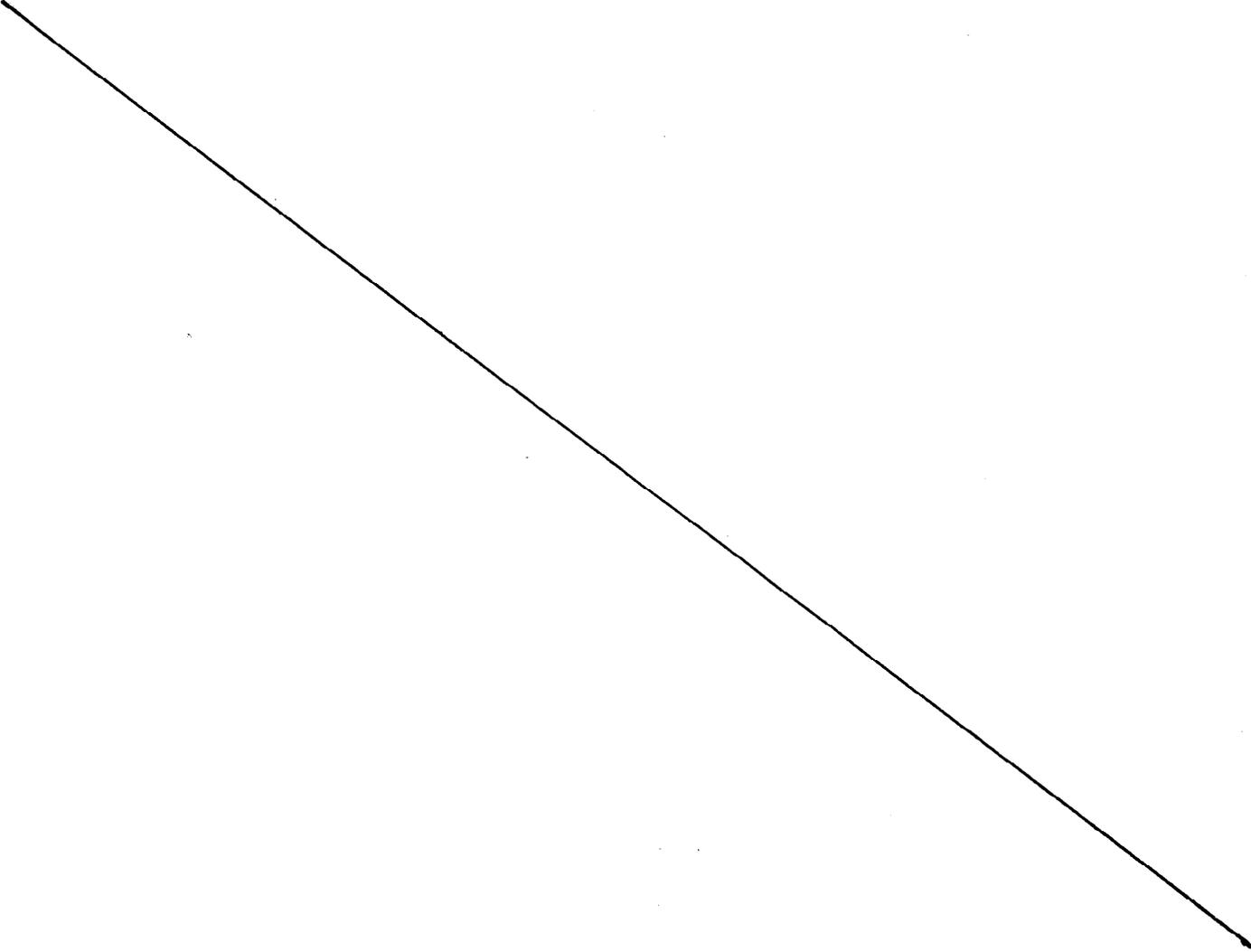
phosphate tablets. Its suitability petition was approved on May 8, 1986. Roxane's acetaminophen and codeine phosphate tablets, 500 mg/15 mg, 500 mg/30 mg, and 500 mg/60 mg, are the subject of ANDAs 89-511, 89-512, and 89-513, respectively. FDA approved ANDAs 89-511, 89-512, and 89-513, held by Roxane, on April 24, 1989, at which time they became "listed drugs" within the meaning of 21 CFR 314.3. On October 23, 1997, Roxane requested withdrawal of approval of ANDAs 89-511, 89-512, and 89-513. FDA withdrew approval of these ANDAs on June 11, 1998.

On July 23, 2001, Aspire Pharmaceuticals, Inc., submitted a citizen petition (Docket No. 01P-0315/CP1) under 21 CFR 10.30 to FDA requesting that the agency determine whether Roxane's acetaminophen and codeine phosphate tablets, 500 mg/15 mg, 500 mg/30 mg, and 500 mg/60 mg, were withdrawn from sale for reasons of safety or effectiveness.

The agency has determined that Roxane's acetaminophen and codeine phosphate tablets, 500 mg/15 mg, 500 mg/30 mg, and 500 mg/60 mg, were not withdrawn from sale for reasons of safety or effectiveness. Two grounds support the agency's finding. First, there are drug products with a combination of acetaminophen and codeine phosphate being marketed today with greater than 500 mg of acetaminophen. Second, when FDA's Center for Drug Evaluation and Research Suitability Petition Committee first considered Roxane's suitability petition for its acetaminophen and codeine phosphate drug products, it concluded that the drug products did not need any safety or efficacy studies to support their approval because the proposed change in strength of the acetaminophen component fell within acceptable limits established by the Monograph for Over-the-Counter Internal Analgesic, Antipyretic, and Antirheumatic Drug Products.

After considering the citizen petition and reviewing its records, FDA determines that, for the reasons outlined previously in this document, Roxane's acetaminophen and codeine phosphate tablets, 500 mg/15 mg, 500 mg/30 mg, and 500 mg/60 mg, were not withdrawn from sale for reasons of safety or effectiveness. Accordingly, the agency will continue to list acetaminophen and codeine phosphate tablets, 500 mg/15 mg, 500 mg/30 mg, and 500 mg/60 mg in the

“Discontinued Drug Product List” section of the Orange Book. The “Discontinued Drug Product List” delineates, among other items, drug products that have been withdrawn from marketing for reasons other than safety or effectiveness. ANDAs that refer to acetaminophen and codeine phosphate tablets, 500 mg/15 mg, 500 mg/30 mg, and 500 mg/60 mg, may be approved by the agency .



Dated: 4/29/02
April 29, 2002.



Margaret M. Dotzel,
Associate Commissioner for Policy.

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