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**DEPARTMENT OF HEALTH AND HUMAN SERVICES**

**Food and Drug Administration**

[Docket Nos. 92P-0274 and 97P-0437]

**Determination That Bendectin Was Not Withdrawn From Sale for Reasons of Safety or Effectiveness**

**AGENCY:** Food and Drug Administration, HHS.

**ACTION:** Notice.

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**SUMMARY:** The Food and Drug Administration (FDA) has determined that the drug product Bendectin, a tablet composed of pyroxidine hydrochloride, 10 milligram (mg), and doxylamine succinate, 10 mg, for the prevention of nausea during pregnancy was not withdrawn from sale for reasons of safety or effectiveness. This determination will permit FDA to approve abbreviated new drug applications (ANDA's) for the combination product pyroxidine hydrochloride, 10 mg, and doxylamine succinate, 10 mg, tablets.

**FOR FURTHER INFORMATION CONTACT:** Andrea C. Masciale, 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 approved innovator drug products under an ANDA procedure. ANDA sponsors generally must 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 a drug that was previously approved under a new drug application (NDA). Sponsors of ANDA's are not required to repeat the extensive clinical testing necessary to gain approval of an NDA.

The only data from investigations 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.” Although they are technically drugs that should be listed under section 505(j)(7) of the act, certain drug products, including Bendectin, that were approved for safety and effectiveness but were no longer marketed on September 24, 1984, are not included in the Orange Book. In implementing the 1984 amendments, FDA decided not to retrospectively review products withdrawn from the market prior to the passage of the amendments. Rather, the agency decided to determine whether such drugs were withdrawn from the market for safety or effectiveness reasons on a case-by-case basis. A person interested in obtaining marketing approval for such a drug product through the ANDA process must petition the agency for a determination (21 CFR 314.122(d)).

Under FDA’s regulations, drugs are withdrawn from the list if the agency withdraws or the Secretary of Health and Human Services 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). FDA must make a determination as to whether a listed drug was withdrawn for reasons of safety or effectiveness when a person petitions for such a determination (§ 314.161(a)(3) (21 CFR 314.161(a)(3))). Regulations also provide that the agency must make a determination as to 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 (§ 314.161(a)(1)). FDA may not approve an ANDA that does not refer to a listed drug.

Bendectin is the subject of approved NDA 10–598, currently held by Hoechst Marion Roussel, Inc. (HMR). In 1956, FDA approved the NDA for Bendectin tablets for use in the prevention

of nausea during pregnancy. The original formulation of the antinauseant included dicyclomine hydrochloride, pyroxidine hydrochloride, and doxylamine succinate. The drug was reviewed in the agency's Drug Efficacy Study Implementation program, in which FDA concluded that dicyclomine hydrochloride did not contribute to the effectiveness of the other two ingredients in Bendectin tablets. Therefore, the drug product was reformulated in 1976 to include only pyroxidine hydrochloride, 10 mg, and doxylamine succinate, 10 mg.

On June 9, 1983, Merrell Dow, HMR's predecessor in interest, withdrew Bendectin tablets from sale in the United States and worldwide. Other companies have continued to market this product in other areas of the world. To FDA, to the press, and in letters to customers using Bendectin tablets, Merrell Dow, in explaining its decision, stated that the withdrawal of the drug product was due to nonmedical reasons, noting significant adverse publicity and the burdens of litigation. At the same time, Merrell Dow asserted its view that "available medical evidence does not demonstrate a cause and effect relationship between the use of Bendectin and birth defects." In an FDA Talk Paper issued on the day Bendectin was withdrawn from sale, the agency stated that Merrell Dow's decision was "independent" of action by FDA. HMR and predecessors in interest to HMR have continually maintained that the withdrawal of Bendectin tablets was for reasons other than safety or effectiveness.

On June 24, 1992, Townley & Updike, on behalf of Pharmaceutical Development and Licensing, Inc., submitted a citizen petition under 21 CFR 10.30 (Docket No. 92P-0274/CP1) regarding the status of Bendectin. A similar citizen petition was filed by Cato Research on behalf of Duchesnay Inc., on October 20, 1997 (Docket No. 97P-0437/CP1). Both petitions request that the agency determine whether Bendectin was withdrawn from sale for reasons of safety or effectiveness and, if the agency determines that the drug was not withdrawn from sale for reasons of safety or effectiveness, relist the drug in the Orange Book.

Under § 314.161, the relevant inquiry is whether the manufacturer withdrew the drug from the market for reasons of safety or effectiveness. Where, as here, a substantial amount of time

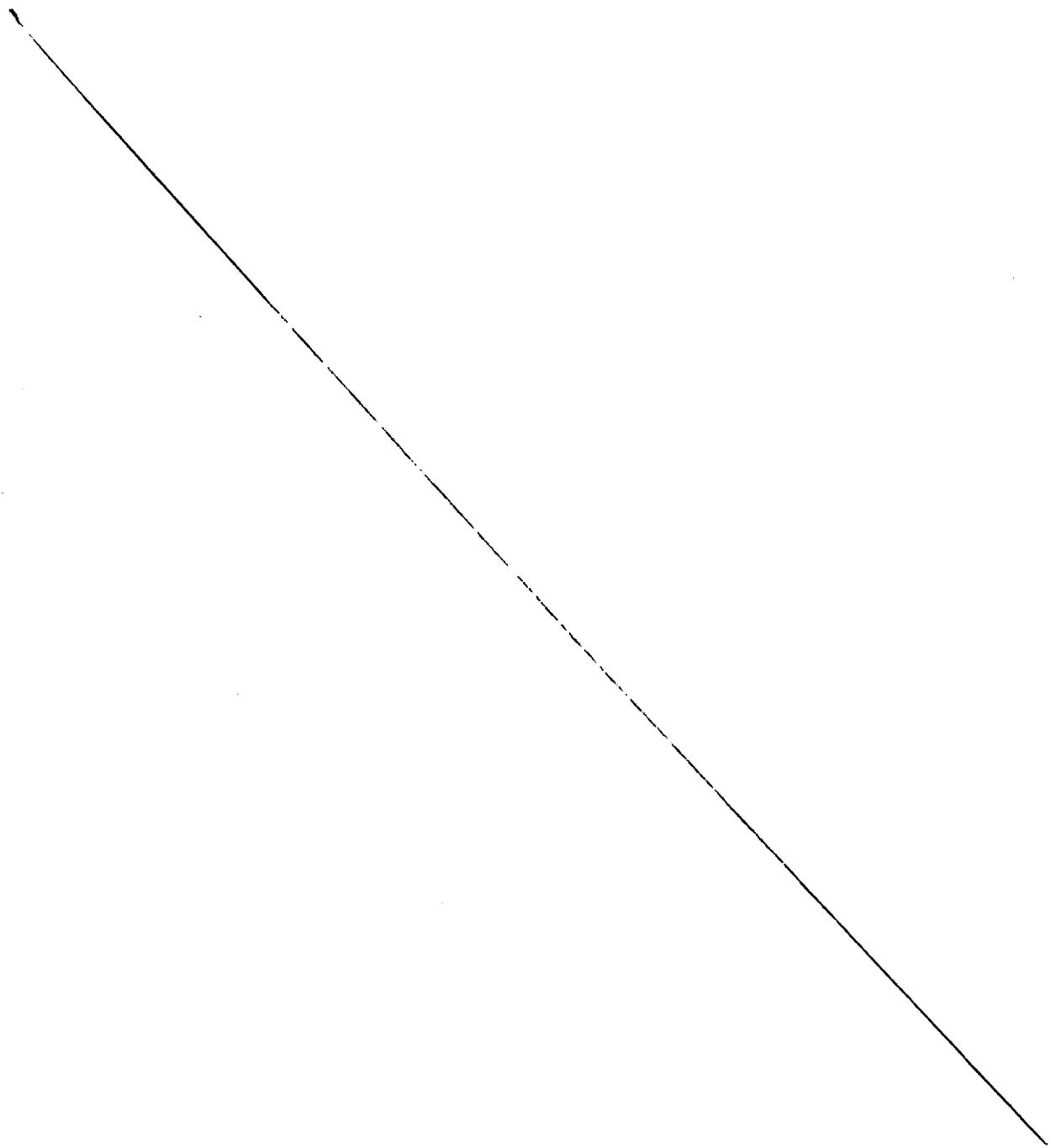
has elapsed since a drug was withdrawn from the market, the agency's inquiry considers not only the reasons the manufacturer initially ceased marketing the product, but also any relevant information that has become available since the market withdrawal. Because a finding that a product was not withdrawn for safety or effectiveness reasons will permit the approval of ANDA's for the drug, the agency considers all relevant information, not just information available at the time of the initial withdrawal, to determine whether a drug is no longer on the market due to safety or effectiveness concerns.

The agency's review of the withdrawal of Bendectin from the market has considered the sponsor's explanation of the basis for the withdrawal of the product in 1983 and information available to the agency regarding safety or effectiveness concerns for Bendectin. As noted previously, the sponsor has consistently maintained that it withdrew Bendectin from the market for reasons other than safety or effectiveness. The agency has reviewed information submitted with the petitions, published studies, U.S. and foreign adverse event reports, and FDA records. The current evidence supports the conclusion that Bendectin was not withdrawn from the market for reasons of safety or effectiveness.

Doxylamine succinate is an active ingredient in several over-the-counter (OTC) antihistamines and sleep aids. The labeling of these OTC products bears statements that pregnant women should seek the advice of a health professional before using the products or that the products should not be taken by pregnant women. These statements do not contradict FDA's present determination because the combination product pyroxidine hydrochloride, 10 mg, and doxylamine succinate, 10 mg, is a prescription drug product. As with all prescription drug products that are being considered for use in a pregnant woman, a health professional may appropriately assess the risks and benefits of pyroxidine hydrochloride and doxylamine succinate for its intended use.

Pyroxidine hydrochloride is also known as vitamin B<sub>6</sub>. As an individual product, it is readily available to U.S. consumers without the requirement of a prescription.

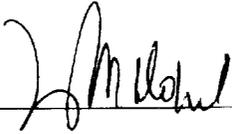
The agency has determined under § 314.161 that Bendectin was not withdrawn from the market for reasons of safety or effectiveness. Accordingly, the agency will list Bendectin tablets in the “Discontinued Drug Product List” section of the Orange Book. The “Discontinued Drug Product List” delineates, among other items, drug products that have been discontinued from marketing



for reasons other than safety or effectiveness. ANDA's that refer to the combination product pyroxidine hydrochloride, 10 mg, and doxylamine succinate, 10 mg, tablets may be approved by the agency.

Dated: 7/28/99

July 28, 1999



Margaret M. Dotzel  
Acting Associate Commissioner  
for Policy

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