DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

AUG 15 2013

Ms. Betty Mekdeci
Birth Defect Research for Children, Inc.
976 Lake Baldwin Lane, Suite 104
Orlando FL 32814

RE: FDA-1992-P-0494

Dear Ms. Mekdeci:

This letter responds to your citizen petition received on May 27, 1992, and submitted on behalf of the Association of Birth Defect Children, Inc. (now Birth Defect Research for Children, Inc.), the National Network to Prevent Birth Defects, the Association for Children and Adults with Learning Disabilities, Inc., and Parents Against Leukemia and Cancer, Inc. (Petition). You request that the United States Food and Drug Administration (FDA or the Agency) withdraw marketing approval for doxylamine succinate (doxylamine) because of positive cancer studies in animals and epidemiological studies showing an increase in childhood cancers in the children of women who took doxylamine during pregnancy.[1]

FDA has considered the information submitted in the Petition and other relevant data. Based on our review of this information, and for the reasons described below, the Petition is denied.

I. BACKGROUND

Doxylamine has been used as an active ingredient in both prescription and non-prescription (OTC) medications in the United States since 1948.[2] Doxylamine is the active ingredient in prescription medications indicated for the treatment of nausea and vomiting during pregnancy, and in OTC antihistamines and nighttime sleep-aids. Currently, doxylamine is an active ingredient in the prescription drug Diclegis (doxylamine succinate and pyridoxine hydrochloride), which is indicated for the treatment of nausea and vomiting of pregnancy in women who do not respond to conservative management.[3] Doxylamine is also listed as an antihistamine active ingredient in the final monograph for Cough, Cold, Allergy, Bronchodilator, and

[1] Petition at 2 - 3.
[2] Doxylamine was first approved as safe by FDA on April 7, 1948, as Decapryn (doxylamine succinate 12.5 milligrams (mg) and 25 mg syrup and tablets for relief of symptoms of the common cold. See http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.DrugDetails. The effectiveness of Decapryn was confirmed in the *Federal Register* on March 19, 1973 (38 FR 7265).
[3] Diclegis was approved on April 8, 2013, see http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.DrugDetails.

Antiasthmatic Drug Products for Over the Counter Human Use (OTC antihistamine final monograph), 21 CFR Part 341.[4] Doxylamine is also approved and marketed as an OTC nighttime sleep-aid.[5] The Agency has confirmed on multiple occasions that doxylamine is safe and effective for its intended uses.

II. DISCUSSION

Your request that FDA withdraw doxylamine from the market is based largely upon the results of animal studies and epidemiological case-control studies that examined the carcinogenicity of doxylamine in patients and their offspring, respectively. The Petition describes the results of a 1991 technical report from the National Center for Toxicological Research (NCTR) concerning a two-year carcinogenicity and chronic toxicity study of doxylamine.[6] You also cite five journal articles regarding epidemiological evidence of childhood cancers associated with doxylamine use during pregnancy.[7]

In June 1991, the Pulmonary-Allergy Drugs Advisory Committee (P-A Committee) met to discuss the NCTR report cited in the Petition. By a vote of 5 to 1, the P-A Committee concluded that "the human carcinogenic potential of doxylamine is not likely" and that doxylamine should continue to be available for OTC use, but also noted that the Agency might want to consider noting the results of the NCTR report in the labeling of OTC products containing doxylamine.[8] The Agency asked the Nonprescription Drugs Advisory Committee (NDAC) to consider whether such information should be included in the labeling for OTC products containing doxylamine.

The NDAC met in June 1993. At that meeting, you presented the five epidemiology articles referenced in the Petition, and received feedback from the NDAC on the validity of the evidence presented in each article. The NDAC noted, "some didn't show carcinogenicity and those that had a high odds-ratio had the 95 percent confidence interval so close to 1 that it is not convincing.[9] In addition, methodologically, only two of the five papers controlled for smoking at all and none of them at all controlled for passive smoking, two well-known carcinogenic situations."[10] The NDAC considered

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[4] 59 FR 4216 (January 28, 1994).

[5] On October 18, 1978, FDA approved a New Drug Application for Unisom (doxylamine succinate, 25mg) see http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.Label_ApprovalHistory#apphist.

[6] Petition at 4-5.

[7] Petition at 6-7.

[8] In the *Federal Register* of December 9, 1992, FDA issued a Final Monograph for OTC antihistamine drug products. Doxylamine was not included in the OTC antihistamine final monograph because the Agency was still evaluating the NCTR report. However, doxylamine was allowed to remain on the market under the 1988 Tentative Final Monograph for Cough, Cold, Allergy, Bronchodilator, and Antiasthmatic Drug Products for Over the Counter Human Use. 57 FR 58356 at 58357 (December 9, 1992).

[9] A confidence interval of 1 is interpreted as showing no effect, or no statistical significance.

[10] Transcript of the June 28, 1993, meeting of the FDA Non-Prescription Drugs Advisory Committee (NDAC Transcript), vol. II, at 165.

your articles, as well as the NCTR report, when making its recommendations.[11] In a 1994 *Federal Register* notice, the Agency adopted the NDAC's unanimous (10 to 0) recommendation to reaffirm the P-A Committee's recommendation that doxylamine remain an OTC drug. The Agency also adopted the NDAC's unanimous recommendation (10 to 0) that there be no specific statement about the results of the NCTR report in the labeling of OTC antihistamine products containing doxylamine.[12] In this same notice, the Agency announced its determination that doxylamine is generally recognized as safe and effective (GRASE) for use as an antihistamine and should be included in the OTC antihistamine final monograph.[13]

In addition, in 1999, FDA determined that the prescription drug, Bendectin, (doxylamine succinate and pyridoxine hydrochloride) was not withdrawn for reasons of safety and effectiveness.[14] When the Agency issued its determination, it publicly and carefully considered all of the available data regarding the safety and effectiveness of doxylamine, including the safety concerns raised in the Petition.

More recently, in April 2013, FDA approved the prescription drug, Diclegis, for the treatment of nausea and vomiting of pregnancy in women who do not respond to conservative management.[15] FDA approved Diclegis after reviewing the results of

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[11] NDAC Transcript, vol. II, at 163-165.

[12] 59 FR 4216. Following a recommendation by the NDAC, the Agency issued a talk paper in 1994 regarding the results of the NCTR report. In the Talk Paper, FDA microbiologist Katharine Freeman noted that the results of the NCTR report were "inconclusive" and that "it was impossible to say if the changes seen in some animals – like tumors and liver toxicity – were species-specific, or if the findings were relevant to human use." See Segal, Marian, "OTC options: help for the sleepless – over-the-counter sleep-aids – includes related articles on doxylamine and sleep techniques," FDA Consumer, September 1, 1994, available at http://the-medical-dictionary.com/doxylamine_article_1.htm.

[13] 59 FR 4217.

[14] Bendectin was a prescription medication indicated for the treatment of nausea and vomiting during pregnancy. Bendectin (10 mg doxylamine succinate, 10 mg pyridoxine hydrochloride, and 10 mg dicyclomine hydrochloride) delayed release tablets was approved originally on July 30, 1956, for the treatment of "nausea and vomiting of pregnancy which are unresponsive to conservative measures such as eating soda crackers or drinking hot and cold liquids, which interfere with normal eating habits or daily activities, and are sufficiently distressing to require drug intervention." In 1972, as part of the Agency's Drug Efficacy Study Implementation (DESI) review, FDA published its determination that Bendectin was possibly effective for the treatment of nausea and vomiting in pregnancy (37 FR 13489 (July 8, 1972)). In 1974, FDA published a *Federal Register* notice stating that "in view of the fact that [Bendectin] is the only product on the market indicated for nausea and vomiting of pregnancy, the Commissioner concludes that it may remain available pending completion and review of the studies" being conducted to confirm its efficacy (39 FR 17343 (May 15, 1974)). After a thorough review of the data, on November 9, 1976, FDA approved a reformulated version of Bendectin containing only doxylamine and pyridoxine hydrochloride. In the *Federal Register* of January 28, 1977, FDA published its findings that a fixed-combination of doxylamine and pyridoxine hydrochloride was effective for the treatment of nausea and vomiting of pregnancy (42 FR 5422 (January 28, 1977)). Bendectin remained on the market until June 9, 1983, when it was voluntarily withdrawn by the manufacturer. After a thorough review, the Agency announced in a 1999 *Federal Register* notice its determination that Bendectin was not withdrawn from the market for reasons of safety or effectiveness (64 FR 43910 (August 9, 1999)).

[15] Efficacy and safety data for Diclegis were obtained from a single, randomized, double-blind, multicenter, placebo-controlled, parallel group clinical trial. The Agency also considered supportive safety and efficacy data from the 1976 approval of reformulated Bendectin (10 mg doxylamine succinate and 10 mg pyridoxine hydrochloride), the Agency's 1999 determination that Bendectin was not withdrawn for reasons

clinical trials and other data that showed the drug is safe and effective for its indicated use.

You also express concerns about the effect of doxylamine on bone marrow and nerve cells and its potential to cause cancer.[16] You cite The Complete Guide to Prescription and Non-Prescription Drugs, a home reference book for patients, which does not contain any scientific evidence or data to support your claim.[17] You also cite a 1988 paper by Shelby.[18] The Shelby paper discusses the mutagenicity of certain known human carcinogens in mice and rats, but does not discuss doxylamine. These sources do not provide sufficient evidentiary support that doxylamine is carcinogenic, and we are not aware of evidence or data that would support your claims.

III. CONCLUSION

As noted in the Background section above, the Agency has thoroughly reviewed the safety and effectiveness of doxylamine for both prescription and OTC uses on multiple occasions, including when it determined that doxylamine is a GRASE antihistamine drug and should be included in the OTC antihistamine final monograph,[19] when it concluded in the 1999 relisting determination that Bendectin was not withdrawn for reasons of safety or effectiveness, and, most recently, when it approved Diclegis.

Throughout the Agency's decision making process regarding the regulatory status of OTC and prescription products containing doxylamine, you and other members of the public had the opportunity to comment and participate, and an administrative record was established on which the Agency based its decisions. When the Agency issued its 1999 relisting determination for Bendectin, it publicly and carefully considered all of the available data regarding the safety and effectiveness of doxylamine, including the safety concerns raised in the Petition. The Agency also thoroughly considered the safety and effectiveness of doxylamine when it approved Diclegis in April 2013. Accordingly, the basic issues raised in your Petition have been considered and resolved by the Agency, and our delay in issuing a formal response until now was an oversight.

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of safety or effectiveness, and the safety data for Diclectin (10 mg doxylamine succinate and 10 mg pyridoxine hydrochloride), which is manufactured in Canada by the same sponsor as Diclegis. The pharmacology and toxicology review for Diclegis also considered the NCTR report and determined that doxylamine succinate is not likely to have human carcinogenic potential.

[16] Petition at 7.

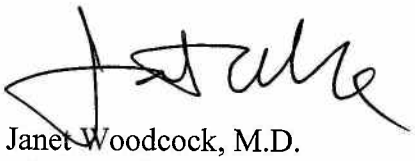
[17] Id.

[18] Id.

[19] 59 FR 4216.

For the reasons described above, the Petition is denied.

Sincerely,



Janet Woodcock, M.D.
Director, Center for Drug Evaluation and Research