DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
College Park, MD 20740-3835

OCT 1 - 2014

K. Paul Stoller, MD, FACHM
(b) (6)

Re: Docket No. FDA-2009-P-0156

Dear Dr. Stoller:

This responds to your citizen petition dated March 13, 2009, as supplemented on October 20, 2010, and January 17, 2011, requesting that the Food and Drug Administration (FDA) revoke the regulation that permits the use of aspartame as a food additive (21 CFR 172.804). You request that the FDA revoke this regulation under the "Delaney amendment" because you believe studies show that aspartame is a carcinogen. For the reasons discussed below, we are denying your petition in accordance with 21 CFR 10.30(e)(3).

BACKGROUND

Section 409(d) of the Federal Food, Drug, and Cosmetic Act (the Act) (21 U.S.C. 348(d)) authorizes FDA to establish regulations prescribing, with respect to any particular use of a food additive, the conditions under which such additive may be safely used.

Under section 409(c)(3)(A) of the Act (21 U.S.C. 348(c)(3)(A)), the so-called "general safety clause" of the statute, a food additive cannot be approved for a particular use unless a fair evaluation of the data available to FDA establishes that the additive is safe for that use. The concept of safety embodied in this requirement was explained in the legislative history of the Food Additives Amendment of 1958. "Safety requires proof of a reasonable certainty that no harm will result from a proposed use of an additive. It does not—and cannot—require proof beyond any possible doubt that no harm will result under any conceivable circumstance." H. Rept. 2284, 85th Cong., 2d Sess. 1 (1958). This concept of safety is incorporated in FDA's food additive regulations (21 CFR 170.3(i)).

The anticancer or Delaney Clause in section 409(c)(3)(A) of the Federal Food, Drug, and Cosmetic Act (the Act) (21 U.S.C. 348(c)(3)(A)) provides that "...no additive shall be deemed to be safe if it is found to induce cancer when ingested by man or animal, or if it is found, after tests which are appropriate for the evaluation of the safety of food additives, to induce cancer in man or animal...."

The food additive uses of aspartame are authorized under 21 CFR 172.804. The regulatory history, including FDA's review of the safety of aspartame, is described in the Commissioner's 1981 final decision (46 FR 38285, July 24, 1981) and in the 1996 final rule that replaced individually listed uses of aspartame with one regulation providing for the safe use of aspartame as a general purpose sweetener (61 FR 33654, June 28, 1996).

YOUR REQUEST

You contend that aspartame is a carcinogen based mainly on the results of three studies that were conducted by the Casare Maltoni Cancer Research Center of the European Ramazzini Foundation (ERF). [1,2,3] However, FDA has not received the full data set for these studies, and would need this data in order to evaluate the results and conclusions from these studies. As you mention in your petition, ERF provided to FDA only limited data and information from the ERF study published in 2006, despite FDA's request for the full set of data from ERF. Without the full data set from the study published in 2006, FDA could not conduct a complete and definitive review of this study. However, based on the available data, FDA concluded that none of the reported histopathological changes appear to be treatment related. Furthermore, the reliability and integrity of the study's results were compromised by significant shortcomings of this study, such as the presence of infection in the test animals. For these reasons, FDA determined that the data that were provided did not support ERF's conclusion that aspartame is a carcinogen.[4, 5] With regard to the study published in 2007, FDA has requested data from ERF but has not received any data. FDA also has not received any data for the ERF study published in 2010.

Your petition discusses potential consumer exposure levels under different scenarios compared to the acceptable daily intake (ADI) of aspartame in the United States. However, your petition did not provide any information showing that the current dietary intake of aspartame for certain individuals exceeds the ADI for the general population. FDA determined the estimated daily intake (EDI) for various age groups by making conservative projections based on data about particular food consumption levels and the amount of additive to be used in particular foods. Using an extremely conservative assumption that aspartame would replace the use of all sugar, FDA estimated that the daily intake would be 8.7 mg/kg bw/day (61 FR 33654, June 28, 1996). This EDI is much lower than the ADI of 50 mg/kg bw/day of aspartame. This conservative exposure estimate shows that high levels of aspartame intake derived for different age groups are unlikely to exceed the ADI if used in food with no limitations other than current good manufacturing practice.

You also contend that GD Searle's original research on aspartame was fraudulent, and that FDA had no intention of approving aspartame because of the fraud. FDA disagrees with this assertion. In early 1976, FDA assembled a team of field investigators headed by Inspector

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[1] Soffritti M, Belpoggi F, Degli Esposti D, Lambertini L, Tibaldi E, Rigano A., "First experimental demonstration of the multipotential carcinogenic effects of aspartame administered in the feed to Sprague-Dawley rats." Environ Health Perspect., 114(3):379-85, Mar 2006.

[2] Soffritti M, Belpoggi F, Tibaldi E, Esposti DD, Lauriola M., "Life-span exposure to low doses of aspartame beginning during prenatal life increases cancer effects in rats," Environ Health Perspect.,115(9):1293-7, Sept 2007.

[3] Soffritti M, Belpoggi F, Manservigi M, Tibaldi E, Lauriola M, Falcioni L, Bua L. "Aspartame administered in feed, beginning prenatally through life span, induces cancers of the liver and lung in male Swiss mice.," Am J Ind Med.;53(12):1197-206, Dec 2010.

[4] FDA Statement on European Aspartame Study. April 20, 2007, http://www.fda.gov/food/ingredientspackaginglabeling/foodadditivesingredients/ucm208580.htm

[5] Memorandum from T. Scott Thurmond, FDA to David H. Hattan, "Review of available data from the Ramazzini Foundation on their end-of-life aspartame study in Sprague Dawley rats." February 28, 2007.

Jerome Bressler of the Chicago District Office with Bureau of Food scientists as advisors. This team examined the facilities, laboratory practices, and data records for three of the studies (E-5, E-89 and E-77-78) that were used to support the safety of aspartame. They inspected the facilities and the raw data records; determined how records were maintained, how animals were kept, how feed was mixed; and interviewed Searle personnel to ensure that the data were recorded as observed and not fabricated. These types of inspections have come to be known as "good laboratory practice inspections." The team wrote up the results of their inspection in two establishment inspection reports (EIRs) dated July 18, 1977 and August 7, 1977. These two EIRs are referred to as the "Bressler Report." The investigators raised questions about some of the laboratory practices they discovered during the field examination. Following the investigation, a task force composed of FDA Bureau of Foods toxicologists was formed to review the Bressler Report. This Bureau of Foods task force found that most of the shortcomings, transcription errors, or changes in the study protocols were not of such magnitude that they would significantly alter the original conclusions of these studies, and that the studies appeared authentic. Thus, while the early investigations of the aspartame studies raised questions about their validity, the detailed examination of the three studies by FDA Bureau of Foods toxicologists determined the study deficiencies to be minor ones, and resulted in the conclusion that the study results were authentic and reliable.[6] After the Universities Associated for Research and Education in Pathology (UAREP) authenticated the remaining 12 studies[7], FDA was confident it could rely on the results of all 15 studies to support the safety of aspartame.

The safety of aspartame has been reviewed repeatedly, not only by FDA, but by other regulatory authorities, including those of Canada, the United Kingdom, Australia, Europe, and Japan. All these authorities agree that aspartame is safe for the general population except for individuals with phenylketonuria. Despite your many assertions, you have not identified any scientific data or other information that would cause the agency to alter its conclusions about the safety of aspartame. Therefore, FDA is denying your petition.

Sincerely,

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Steven Musser, Ph.D.
Deputy Director for Scientific Operations
Center for Food Safety
and Applied Nutrition

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[6] March 16, 1979 Memorandum, "Review of the UAREP Authentication Report on Aspartame Studies."

[7] University Associated for Research and Education in Pathology, Inc. "Authentication Review of Selected Materials Submitted to the Food and Drug Administration Relative to Application of Searle Laboratories to Market Aspartame." November 1978.