DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
College Park, MD 20740-3835

MEMORANDUM

Date: March 18, 2015

To: [redacted] Office of Compliance, HFS-608

From: [redacted] Division of Biotechnology and GRAS Notice Review, Office of Food Additive Safety, HFS-255

Through: [redacted], Director, Division of Biotechnology and GRAS Notice Review, Office of Food Additive Safety, HFS-255

Through: [redacted], Director, Office of Food Additive Safety, HFS-200

Subject: [redacted]

This is in response to your November 17, 2014 memorandum requesting Office of Food Additive Safety (OFAS) review of [redacted] product containing dimethylamylamine (DMAA). You ask if DMAA as contained in the product meets the criterion for an adulteration charge within the meaning of Section 402(a)(2)(C)(i) [21 U.S.C. §342(a)(2)(C)(i)] as a food additive which is not the subject of a food additive regulation under section 409 of the Act [21 U.S.C. 348] and is therefore unsafe.

1. In light of the scientific data and publically-available information, DMAA is not generally recognized as safe (GRAS), and, therefore, is not excluded from the statutory definition of "food additive". (21 U.S.C. §321(s)). There is not general recognition among experts qualified by scientific training and experience to evaluate DMAA's safety, that DMAA has been adequately shown through scientific procedures to be safe under the conditions of its intended use. To the contrary, the publicly-available data indicate that use of DMAA in food is a cause for concern.

   FDA is unaware of any use of DMAA in food prior to 1958; therefore it does not meet the "common use in food" criteria for GRAS and eligibility for GRAS would need to be based on "scientific procedures." To be eligible for GRAS under "scientific procedures," there must be adequate technical evidence of safety and the technical evidence of safety must be generally known and accepted by recognized experts as demonstrative of the safety of the intended use in food.

FDA reviewers searched databases of scientific publications and as of November, 2014 found 25 articles containing the terms 1,3-dimethylamylamine, dimethylamylamine, and/or methylhexaneamine. Of the 25 articles found, six were relevant to a safety assessment and none were relevant to a food safety assessment such as a toxicological study conducted in laboratory animals. FDA's conclusions from its review of the scientific publication databases are that there are few published studies relevant to a safety assessment; none of the publications support safe use, and the few articles that are in the literature raise safety concerns associated with the consumption of DMAA. Below are two recent examples.

a. One article reported on case studies from a military treatment facility in Southern California (Foley et al., 2014). The article describes seven cases involving liver toxicity after consumption of sports supplements containing DMAA. One individual was 45 years of age, while the others were younger ranging in age from 19 to 28. Of the seven cases, 3 were female and 4 male, and the duration of exposure was anywhere from one week to 3 years. Clinical findings included elevated bilirubin and liver enzymes along with other observations such as jaundice, fatigue, and vomiting.

b. Another article reported on a 22 year-old man that had an acute myocardial infarction (Smith et al., 2014). This individual had been taking daily oral doses of Jack3d which contains DMAA and "Phenorex" (a source of *Citrus aurantium*) for three weeks. His myocardial enzymes and isoenzymes (creatine kinase and creatine kinase-MB) were elevated. The patient had tachycardia which was determined to be due to a clot in the proximal left anterior descending coronary artery. The patient was treated successfully and the clot dissolved. The authors state that the dietary supplements may have been responsible for the clot.

2. DMAA does not meet any of the exclusions from the statutory food additive definition. FDA is not aware of any evidence that DMAA is a pesticide chemical residue in or on a raw agricultural commodity or processed food, a pesticide chemical, a color additive, or a new animal drug. DMAA, therefore, does not meet the exclusions from the statutory definition of a food additive set forth in Section 201(s)(1)-(3) and (5) of the FD&C Act, 21 U.S.C. §§ 321(s)(1)-(3) and (5).

3. We are not aware of any information to establish that DMAA is the subject of a prior sanction; therefore, DMAA does not qualify for exclusion from the food additive definition in Section 201(s)(4) of the FD&C Act, 21 U.S.C. § 321(s)(4).

4. Although DMAA is often in or intended for use in dietary supplements, DMAA is not a dietary ingredient of the type described in Section 201(ff)(1) of the FD&C Act, 21 U.S.C. § 321(ff)(1). Thus, DMAA does not qualify for the exclusion from the food additive definition set forth in Section 201(s)(6) of the FD&C Act, 21 U.S.C. § 321(s)(6).[1]

5. DMAA is an unsafe food additive. Under Section 409(a) of the FD&C Act, 21 U.S.C. § 348(a), a food additive (that is not a food contact substance) is deemed to be unsafe unless it meets one of the following two requirements:

a. The food additive and its use or intended use conform to the terms of an exemption for investigational use which is in effect pursuant to Section 409(j) of the FD&C Act, 21 U.S.C. § 348(j); or

[1] [redacted]

b. There is in effect, and the food additive and its use or intended use are in conformity with, a regulation issued under Section 409 of the FD&C Act, 21 U.S.C. § 348, prescribing the conditions under which such additive may be safely used.

6. A "food contact substance" is "any substance that is intended for use as a component of materials used in manufacturing, packing, packaging, transporting, or holding food if such use is not intended to have any technical effect in such food" (21 C.F.R. § 170.3(e)(3)). DMAA, when used in dietary supplements, is not a food contact substance because it is intended to become a component of the food in which it is included.

7. In sum, it is our opinion that DMAA is a food additive under Sections 201(s) of the FD&C Act, 21 U.S.C. § 321(s), because it is not generally recognized, among experts qualified by scientific training and experience to evaluate its safety, as having been adequately shown through scientific procedures to be safe under the conditions of its intended use and it does not meet any of the exclusions set forth in Section 201(s)(1)- (6) of the FD&C Act, 21 U.S.C. §§ 321(s)(1)-(6). It is also our opinion that DMAA is an unsafe food additive under Section 409(a) of the FD&C Act, 21 U.S.C. § 348(a) because no exemption or regulation is in effect governing its safe use.

In summary, the Office of Food Additive Safety considered the regulatory status and available scientific information regarding the safety of DMAA and found no information to establish its use as GRAS. Therefore, DMAA is deemed unsafe under 21 U.S.C. § 348 and, the [redacted] dietary supplement containing DMAA is properly deemed to be adulterated under 21 U.S.C. § 342 (a)(2)(C)(i).

[redacted]
Supervisory Consumer Safety Officer

References

Foley, S. et al. 2014. Experience with OxyELITE Pro and Acute Liver Injury in Active Duty Service Members. Dig Dis Sci. 59:3117.

Smith, T.B. et al. 2014. Acute myocardial infarction associated with dietary supplements containing 1,3-dimethylamylamine and Citrus aurantium. Tex Heart Inst J. 41:70.

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