



APR 30 2009

Mr. Terry Begley
Iovate Health Sciences, Inc.
381 North Service Road, West
Oakville, Ontario Canada L6M 0H4

Dear Mr. Begley:

On March 31, 2009, the U.S. Food and Drug Administration (FDA or the Agency) informed you during a meeting of concerns that the Agency has about liver toxicity associated with the use of multiple versions of the dietary supplement Hydroxycut marketed by your firm under the Iovate and MuscleTech brand names. Based on adverse events reported to FDA, case reports in the peer-reviewed literature, and in a case series described by hepatologists to FDA, the Agency has concluded that the ingestion of the dietary supplement Hydroxycut presents a severe potentially life-threatening hazard to some users. In a telephone conversation on April 29, 2009, between (b)(4) outside counsel for Iovate Health Sciences, Inc., and Mr. Eric Blumberg, Deputy Chief Counsel, Litigation, Office of Chief Counsel, FDA, the Agency explained our conclusions about the safety of your firm's Hydroxycut products¹ and the additional actions that the FDA expected your firm to take in response to the serious public health hazards presented by the Hydroxycut dietary supplements marketed by your firm. Following that call, your counsel advised Mr. Blumberg that the firm had agreed to recall all Hydroxycut products. The information provided by your counsel expanded the scope of your recall to include your drink mixes as well as the caplet products that your counsel had previously indicated to us that you intended to recall.

Hydroxycut products have been marketed by Iovate Health Sciences, Inc (381 North Service Rd. W., Oakville, ON L6M 0H4, Canada) and by Muscletech (Mississauga, Ontario, Canada) and distributed by Iovate Health Sciences USA, Inc. (Blassdell, NY, USA) as weight control, fat-burner, and energy enhancement dietary supplements. Hydroxycut products bear the Iovate or Muscletech Brand names. The products contain a variety of ingredients as well as numerous proprietary blends such as "Hydroxagen Plus," "Hydroxy Tea," "HydroxyTea CF," "Hydroxycut Proprietary Blend," "Max! Liqui-Burn," "Max! Weight-Loss Matrix," "Hydroxycut Hardcore Proprietary Blend Proxyclyene," "Noreidrol Intensity focus Blend," "Lasidrate Delivery Blend," "or Yohimbacore." The products' labels declare minerals and

¹Hydroxycut products, for purposes of this letter, means Hydroxycut Regular Rapid Release caplets, Hydroxycut Hardcore Liquid caplets, Hydroxycut Max Liquid caplets, Hydroxycut Caffeine-Free Rapid Release caplets, Hydroxycut Regular drink packets, Hydroxycut Hardcore drink packets (Ignition Stix), Hydroxycut Caffeine-Free drink packets, Hydroxycut Max drink packets, Hydroxycut Liquid Shots, Hydroxycut Hardcore RTDs, Hydroxycut Max Aqua Shed, Hydroxycut 24, Hydroxycut Carb Control, and Hydroxycut Natural.

herbs as well as extracts from *Garcinia cambogia*, *Guarana*, *gymnema sylvestre*, *Rhodiola rosea*, and *Camellia sinensis*. Prior to 2004, Hydroxycut, contained ephedra or Ma Huang as an ingredient; however, you stated to us in our meeting that by the beginning of 2004, Hydroxycut was ephedra-free. Subsequent to the removal of ephedra, Hydroxycut has undergone numerous formulation changes.

In 2002, the Center for Food Safety and Applied Nutrition's (CFSAN) adverse event reporting system, CAERS, began receiving reports of liver-related illnesses in persons who reported consuming the dietary supplement Hydroxycut capsules/caplets for periods ranging from as short as a week to two (2) months. Since the earlier formulation of Hydroxycut contained ephedra, it was generally believed that the reports of liver injury associated with the use of the product were due either to ephedra or a combination of the ingredients found in the product. However, following the removal of ephedra from Hydroxycut capsules/caplets, CFSAN continued to receive reports of liver injury associated with the use of Hydroxycut capsules/caplets. In addition, CFSAN became aware of reports of Hydroxycut-associated liver toxicity published in the peer-reviewed literature and received communications from independent hepatologists regarding cases of liver toxicity associated with the use of the Hydroxycut capsules/caplets.

Hydroxycut-associated liver toxicity reports in CAERS. To-date, 23 case reports of Hydroxycut-associated liver toxicity have been identified in CAERS for the period 2002 to the present. The number of reports, by event date, is listed below:

<u>Year of event</u>	<u>Number of reports</u>
2002	4
2003	3
2004	6
2005	0
2006	1
2007	6
2008	3
<u>2009</u>	<u>0</u>
Total	23

For cases in which gender was known, 15 (65%) were female. Ages ranged from 20 years to 51 years (median = 29 years). Sixteen cases (70%) were hospitalized. The majority of cases reported no underlying risk factors for liver disease (e.g., no history of viral hepatitis, no HIV infection, no autoimmune diseases). Although the reports vary in detail, several reports describe work-ups that ruled out infectious, autoimmune, and metabolic causes of liver disease. The severity of illness ranged from asymptomatic elevations in serum bilirubin to acute liver failure (one patient received a liver transplant in 2002, a second patient was reportedly waiting for a liver transplant in 2004) to one death. On March 24, 2009, CFSAN

received information regarding the fatal case. The patient was a 20-year-old male who presented to an emergency room on January 19, 2007 in liver failure and hepatic encephalopathy. He was subsequently transferred to a liver transplant center where, in the operating room, he was found to have necrosis of both the large and small intestines. Given these findings, the procedure was aborted and the patient was returned to the intensive care unit. He died on February 12, 2007.

Reports of Hydroxycut-associated liver toxicity in the peer-reviewed literature. To our knowledge, there are four published reports in the peer-reviewed literature that describe liver disease that occurred in six persons following the consumption of Hydroxycut capsules/caplets^{2,3,4,5}.

The aforementioned cases are consistent with the diagnosis of idiosyncratic hepatotoxicity for a number of reasons: the temporal relationship between the consumption of Hydroxycut capsules/caplets and the development of acute liver injury in persons who had no history of known liver disease; the exclusion of other causes of liver disease following extensive work-ups; the resolution of liver injury upon discontinuation of Hydroxycut capsules/caplets; and the development of liver injury is not dose dependent. Also apparent were two distinct patterns of liver injury: cholestatic and necrotic. It is not unusual for a single herbal preparation to produce more than one type of clinicopathologic liver injury⁶.

Discussions with hepatologists. In discussions in March and April 2009 with hepatologists Tse-Ling Fong, M.D. of the University of Southern California, and William Lee, M.D. of the University of Texas Southwestern Medical Center, CFSAN has become aware of these physicians' case series of patients with severe liver disease associated with the use of Hydroxycut capsules/caplets. Two cases from this series, representing additional cases to the ones reported to CFSAN, underwent liver transplantation following acute liver failure.

² Stevens T, Qadri A, Zein NN. Two patients with acute liver injury associated with use of the herbal weight-loss supplement Hydroxycut. *Ann Intern Med* 2005;142:477-8.

³ Jones FJ, Andrews AH. Acute liver injury associated with the herbal supplement Hydroxycut in a soldier deployed to Iraq. *Am J Gastroenterol* 2007;102:2357.

⁴ Dara L, Hewett J, Lim JK. Hydroxycut hepatotoxicity: A case series and review of liver toxicity from herbal weight loss supplements. *World J Gastroenterol* 2008;14:6999-7004.

⁵ Shim M, Saab S. Severe hepatotoxicity due to Hydroxycut: a case report. *Dig Dis Sci* 2009 Feb;54(2):406-8. Epub 2008 Jul 26.

⁶ Miller SC. Safety concerns regarding ephedrine-type alkaloid-containing dietary supplements. *Mil Med* 2004;169:87-93.

Serious non-hepatic adverse events identified in the CAERS database or the literature.

When the CAERS database was queried for other serious adverse events associated with Hydroxycut, cases of seizures, rhabdomyolysis,⁷ and cardiovascular disorders were identified. For example, from 2004 to 2008, the CAERS database received four case reports describing consumers who experienced a seizure following ingestion of Hydroxycut. In one instance, a 26-year-old consumer increased her daily intake of Hydroxycut from 2 to 4 caplets on December 6, 2008. At 2 p.m. that day, following ingestion of the second serving of 2 caplets, the consumer felt tired and lay down. She was found by another person to be having a “seizure” (shaking and drooling). The consumer was taken to the emergency room where a physician told her to discontinue using Hydroxycut.

The case report describing rhabdomyolysis involved a 23-year-old male who had been consuming Hydroxycut on and off over an eight-month period in 2002. On the day of hospital admission, he had taken 2 tablets for energy prior to working out. He reported feeling nausea, and then several hours later, he had severe shoulder pain and dark urine. He was diagnosed as having rhabdomyolysis on admission to the hospital. In addition to this CAERS report, CFSAN is aware of one case of Hydroxycut capsules/caplets-associated rhabdomyolysis reported in the peer-reviewed literature. In this report, Dehoney and Wellen described an 18-year-old male who experienced rhabdomyolysis after consuming Hydroxycut as per the product’s instructions. During his overnight hospitalization, he received 6 liters of fluid before discharge.⁸

The Agency also identified 46 reports in CAERS of Hydroxycut capsules/caplets-associated cardiovascular adverse events. These events ranged in severity from palpitations to a heart attack. Nineteen of these reports were received during or after 2004, a period when Hydroxycut’s formulation was believed to be free of ephedra.

Conclusion:

Three lines of evidence derived from multiple disparate sources suggest it is very likely that exposure to Hydroxycut capsules/caplets can cause idiosyncratic hepatotoxicity. First, many of the subjects described in the adverse event reports to CAERS, in the peer-reviewed literature, and in the case series described by hepatologists reported no history of liver disease or risk factors for liver disease (e.g., alcohol consumption, previous viral infection, hereditary factors, etc.) prior to experiencing liver injury following the ingestion of Hydroxycut capsules/caplets. Second, in many subjects, thorough diagnostic evaluations performed in multiple settings ruled out a number of known causes of liver disease, including viral

⁷An acute, fulminating, potentially fatal disease of skeletal muscle that entails destruction of skeletal muscle as evidenced by myoglobinemia and myoglobinuria (Stedman’s Medical Dictionary, 26th ed., Williams & Wilkins, Baltimore; 1995).

⁸ Dehoney S, Wellein M. Rhabdomyolysis associated with the nutritional supplement Hydroxycut. *Am J Health Syst Pharm* 2009 Jan 15;66(2):142-86.

hepatitis, autoimmune diseases, and metabolic/inherited disorders. Third, prompt resolution of liver disease occurred in a number of patients following cessation of Hydroxycut capsules/caplets ingestion. While some adverse event reports involved users who had consumed more than the daily dosage recommended on the products' labeling, if these reports were excluded from consideration, the remaining evidence demonstrates liver-related adverse effects following exposure to Hydroxycut capsules/caplets. In addition to Hydroxycut capsules/caplets-associated liver-related adverse effects, CFSAN is aware of a number of CAERS reports that describe seizures, rhabdomyolysis, and cardiovascular signs and symptoms.

The Agency does not know which ingredient(s) of Hydroxycut formulations are responsible for producing liver toxicity. In addition, there is insufficient information to determine whether there is a dose-response effect between Hydroxycut capsules/caplets ingestion or whether its effects are cumulative over time. However, based on the totality of evidence presented above, the Agency concludes that the ingestion of the dietary supplement, Hydroxycut, presents a severe potentially life-threatening hazard to some users. Although Hydroxycut-induced hepatotoxicity has been reversible in most patients that have come to the attention of CFSAN, in certain instances acute liver failure has resulted that has required liver transplantation for survival; death occurred in one instance prior to transplantation.

While the firm believes that the lack of reported adverse events associated with the use of the Hydroxycut shot product and the drink mixes is evidence that they are safe, FDA disagrees. The reports of acute liver injury in individuals who have consumed Hydroxycut capsules/caplets represent idiosyncratic reactions, meaning that the injuries have occurred as a result of conditions peculiar to the affected individuals. As such, the incidence of injuries of this nature is unpredictable and may result from peculiar metabolic interactions between one or more Hydroxycut ingredient and the host's physiologic system. There are no data to indicate that the dose or duration of use of any particular Hydroxycut ingredient, or the gender, or any other identifiable trait of a Hydroxycut user predicts the risk of an adverse event. In light of this, and because the fact that the drink mixes and 'shot' products share ingredients with products known to be associated with adverse events, and because it is unknown which ingredient(s) of Hydroxycut are responsible for producing the idiosyncratic reactions, we believe that the reasonable conclusion to be drawn is that these products present the same risks as the Hydroxycut capsules/caplets.

Given the seriousness of the hazard presented by Hydroxycut, Iovate Health Sciences, Inc. voluntarily agreed to the following:

1. To cease distribution of all existing formulations of Hydroxycut.
2. To recall from the marketplace, to the consumer/user level, all existing formulations of Hydroxycut.

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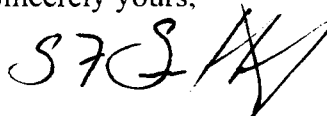
As we stated above, the ingestion of the dietary supplement Hydroxycut presents a severe potentially life-threatening hazard to some users. FDA considers the recalled products to be adulterated under section 402(f)(1)(A) of the Federal Food, Drug, and Cosmetic Act [21 U.S.C. § 342(f)(1)(A)] (the Act) in that the dietary supplements present a significant or unreasonable risk of illness or injury under conditions of use recommended or suggested in labeling.

The New York District Office will be monitoring the recall. The New York District Recall Coordinator is Maria Caride. She can be contacted at (718) 662-5447.

We are aware that Iovate Health Sciences, Inc. plans to reformulate the Hydroxycut product line. As discussed above, we have been unable to identify which specific ingredient or combination of ingredients can be identified as the cause of the hepatotoxicity, cardiotoxicity, seizures, or rhabdomyolysis associated with the use of the existing formulations. Under the Act, you are responsible for ensuring that a dietary supplement you market is safe within the meaning of the Act. We expect that any reformulated Hydroxycut products that contain any of the ingredients present in the existing Hydroxycut formulations would be the subject of a rigorous safety review and that a determination that the formulation(s) of the new products do not present a significant or unreasonable risk or illness or injury under the conditions of use recommended or suggested in labeling is supported by scientific evidence. We suggest that sharing the safety evaluation for the new formulation(s) with FDA will enable us to better respond to inquiries we receive concerning the safety of the new formulation(s). Further, unless each ingredient used in your new formulation(s) is affirmatively documented to have been marketed as a dietary ingredient in the United States before October 15, 1994, you may be required to submit to FDA the notification required by 21 U.S.C. § 350b(a)(2) and 21 CFR § 190.6 at least 75 days before the reformulated product(s) are introduced into interstate commerce. If you believe you do not need to submit a 75 day notification, please provide FDA with documentation to support your determination.

Should you have any questions or comments about the contents of this letter or any aspects of your responsibilities pertaining to the marketing of your products, you may contact Dr. Vasilios Frankos at (301) 436-2375.

Sincerely yours,



Stephen F. Sundlof
Director
Center for Food Safety
and Applied Nutrition

cc: (b)(4)