DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

The Honorable Richard J. Durbin
United States Senate
Washington, D.C. 20510-1304

NOV 21 2012

Dear Senator Durbin:

Thank you for your letters of September 11 and October 26, 2012, co-signed by Senator Richard Blumenthal, in which you indicated that not all of your concerns regarding "energy drinks" were addressed in the response from the Food and Drug Administration (FDA or the Agency) dated August 10, 2012.

You asked for additional information on potential interactions and cumulative effects of multiple additives with stimulant properties in "energy drinks" with caffeine and on health risks associated with consuming high levels of caffeine among young people. Further, you asked that we explain how FDA determines the distinction between flavoring uses and non-flavoring uses of ingredients, including those with purported stimulant properties, and asked that we regulate the level of caffeine in "energy drinks" marketed as beverages.

You raise important issues, and we appreciate the opportunity to address your concerns.

As you know, "energy drinks" containing caffeine and other ingredients are a relatively new class of products. Although these products have the potential to raise safety or regulatory issues, there is a long history of safe use of other caffeine-containing products in the United States. FDA is aware, however, that new products and patterns of use require us to remain vigilant, and we are working to strengthen our understanding of the nature of "energy drinks" and any causal risks to health.

In particular, we are looking at whether products that may be safe for most individuals under labeled-use conditions may pose significant risks, arising from direct toxic effects, when the products are consumed in excess or by vulnerable groups, including young people and those with pre-existing cardiac or other conditions. This review includes investigating as fully as possible reported deaths and other serious adverse events that these reporting parties have associated with energy drinks. In general, FDA does not have the authority to require the production of medical records by families or health care providers, but we are requesting that such records be provided on a voluntary basis, even as we remain sensitive to the wishes of families and the constraints under which health care providers operate in light of state and local laws governing disclosure.

We believe that this review may be greatly enhanced by also engaging specialized expertise outside FDA, most likely through consultation with the Institute of Medicine as well as possibly through an Advisory Committee or other public meeting. Areas of particular focus would include such matters as the vulnerability of certain populations to stimulants and the incidence and consequences of excessive consumption of "energy drinks," especially by young people.

In your letter of October 26, 2012, you reiterated the concerns expressed in your earlier letters and urged FDA to complete a guidance that would clarify for industry the line between dietary supplements and conventional foods and beverages. We are committed to finalizing the draft guidance as rapidly as possible.

In the meantime, we hope the following information helps answer the questions you have raised.

Potential Interactions and Cumulative Effects

You asked about the safety of ingredients with stimulant properties in combination with caffeine in "energy drinks." Ordinarily, FDA evaluates the safety of ingredients for beverages and other conventional foods (including "energy drinks" represented as beverages, which are conventional foods) through food additive premarket programs that generally focus on individual ingredients that may be used in a range of food, rather than on a product-specific basis. FDA does not have the authority to require a manufacturer to submit each formulated product for premarket review. For each food ingredient, however, there must be information to assess how much of the ingredient humans will likely consume in their diet, as well as information to show that the ingredient is safe to consume at that estimated dietary intake and under intended conditions of use. Certain ingredients are exempt from these food additive premarket approval requirements. For example, those ingredients which are generally recognized as safe (GRAS) for the intended conditions of use, as well as those substances that are prior sanctioned, are exempt.

FDA agrees that additive or synergistic effects of certain ingredients could be of concern. Thus, in the case of stimulants, if the intended conditions of use include combined use with other stimulants and that combination raises a significant safety question, FDA could require data addressing the combination to inform premarket safety reviews, including to support determinations of GRAS status.

A major limitation in assessing the toxicity of combinations of ingredients, whether by commercial sponsors or by FDA, is related to the vast number of potentially relevant combinations of ingredients and use levels that could be tested. Resource and capacity constraints preclude government or government-funded toxicity testing of all but a very small number of the possible combinations. Although FDA has yet to identify any safety studies that call into question the safety of combinations of various ingredients added to "energy drinks" under intended conditions of use, if we determine that any such combinations are of concern in our continuing review of "energy drinks," we will

consider regulatory actions as well as other options, such as conducting needed scientific studies.

Safety of Flavoring Versus Non-flavoring Uses of Ingredients with Purported Stimulant Properties

For ingredients added to products marketed as beverages, regardless of the technical effect in the food (flavor or otherwise), the safety standard is a reasonable certainty of no harm. Many substances used as flavorings are GRAS. It is possible for a substance to be GRAS for use as a flavor at one level (or concentration) and GRAS for another use at a different level, provided that the GRAS standard in section 201(s) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) is met in each case.

Under the FD&C Act, in evaluating the safety of an ingredient added to food, claims regarding purported benefits of any type are not considered. The safety decision for a food ingredient is not based on an analysis of risk versus benefit but is based on safety alone. The technical effect of a conventional ingredient comes into play as a regulatory matter when FDA determines that a tolerance for the ingredient is necessary to ensure safety, with tolerances required under the FD&C Act's food additive provisions to be set at a level that ensures safety and is no higher than needed to achieve an intended technical effect (section 409(c)(4)(A)).

With respect to taurine and guarana (flavoring substances mentioned in your letter), FDA searched the literature but did not find any information that calls into question the safety of these ingredients as currently used in beverages. Thus, to date, FDA has made no determination with respect to the intended technical effect of their use in "energy drinks," which may include both flavoring and stimulant effects. But if, in the course of our surveillance, we learn of information raising safety concerns about the use of these substances, we will evaluate it and determine whether enforcement or other regulatory action is needed to protect the public health.

Regulation of Caffeine and Other Ingredients with Stimulant Properties in Dietary Supplements

If a dietary ingredient has been listed or affirmed by FDA as GRAS for direct addition to food, self-affirmed as GRAS for addition to food, or approved as a food additive in the United States, the manufacturer or distributor of the dietary ingredient or dietary supplement is not generally required to provide FDA with a new dietary ingredient (NDI) notification, as long as the substance has been used in the food supply prior to 1994, is to be used without chemical alteration, and is not combined with an NDI.

For a dietary supplement that contains an NDI that has not been present in the food supply as an article used for food, in a form in which the food has not been chemically altered, the manufacturer or distributor of the dietary ingredient or dietary supplement must provide FDA with certain information in the form of an NDI notification, pursuant to section 413(a)(2) of the FD&C Act. The information is to include copies of any

published articles that serve as the basis on which the firm has concluded that a dietary supplement containing such NDI will reasonably be expected to be safe. All NDIs are subject to the adulteration standard in section 402(f)(1)(B) of the FD&C Act, which requires adequate information to provide reasonable assurance that the ingredient does not present a significant or unreasonable risk of illness or injury.

Under the FD&C Act, dietary supplements that do not contain NDIs are not subject to premarket review by FDA. Thus, the Agency must depend on post-market surveillance, e.g., Adverse Event Reports (AERs), to determine the potential for interactions and cumulative effects of ingredients with stimulant properties in dietary supplements with caffeine. In evaluating AERs for dietary supplements, FDA must also consider the use of the product as described in labeling. Energy supplements frequently bear warning statements regarding the nature of the ingredients as well as recommended consumption amounts and frequency of use. For example, for FDA to find that a specific dietary supplement is adulterated under section 402(f)(1)(A) of the FD&C Act, the dietary supplement (or a dietary ingredient in that supplement) must present a significant or unreasonable risk of illness or injury under the conditions of use recommended or suggested in labeling (e.g., "do not use more than one can per day," "not to be used by those under 18"), or ordinary conditions of use if no conditions of use are suggested or recommended in the labeling. This statutory framework constrains FDA's ability to take regulatory action when a product is consumed to excess or otherwise used in a manner that contradicts the labeled recommendations and warnings.

Age-Related Health Concerns

You stated that in our August 10 response, FDA did not adequately address the potential health risks associated with young people consuming high levels of caffeine. You further stated that FDA did not assess the shifting consumption patterns among young people, who are major drinkers of "energy drinks." In an effort to better understand consumption patterns for potentially susceptible subgroups, FDA contracted for the performance of an in-depth analysis of the caffeine consumption by the U.S. population, which was completed in September 2009 and revised in August 2010 (Somogyi 2010).[1] We are enclosing a copy of this report for your information.

This report indicates that the mean amount of caffeine consumed by the U.S. population is consistent with past FDA estimates, remaining relatively stable at approximately 300 milligrams per person per day (mg/p/d), despite the entry of "energy drinks" into the market place (see Figure 12, page 68 of the report). Significantly, this report also indicates that teens and young adults (14-21 years of age) consume, at the mean, approximately one-third (or about 100 mg/p/d) the amount of caffeine as adults, and that their caffeine consumption is mainly from coffee, soft drinks, and tea.

According to the report, "energy drinks" contribute a small portion of the caffeine consumed, even for teens. Table 33 of Somogyi 2010 (page 63) shows the breakout of

[1] Caffeine Intake by the U.S. Population, September 2009, revd. August 2010, by Laszlo P. Somogyi, Ph.D.

components of the overall exposure to caffeine for teens.[2] Coffee contributes 25 mg for boys and 34 mg for girls; teas, 25 mg for boys and 16 mg for girls; carbonated beverages, 45 mg for boys and 36 mg for girls; other beverages, 12 mg for boys and 15 mg for girls. We recognize the limitations of these data as with any survey of this nature, including the fact that the data do not reveal possible extremes of consumption by individuals, which, alone or in conjunction with other factors, could pose health risks. Nevertheless, these data do contribute to our general understanding of caffeine consumption by potentially susceptible subgroups at the time the data were collected. We also recognize the need to take into account how consumption patterns and intakes may be changing with the growing consumption of "energy drinks" and other caffeinated products.

As you pointed out, FDA's August 10 letter noted that caffeine consumption of 400 mg per day in healthy adults is not associated with adverse effects on various parameters. We would like to provide additional context around this consumption value. This value reflects the recommended upper level of caffeine consumption by Health Canada, which was based on its review of the data in 2003 (Nawrot et al., 2003).[3] However, there is a great deal of variability in the population, with respect to caffeine sensitivity and caffeine tolerance, making it difficult to define a value that would apply to the entire population. For example, body weight has a large impact on the effects of caffeine consumption, with smaller individuals typically more sensitive if they are not caffeine-tolerant. The United Kingdom's Food Standards Agency recommends that pregnant women consume no more than 200 mg caffeine per day (COT, 2008).[4]

You cited a recommendation by the American Academy of Pediatrics of no more than 100 mg caffeine/day for adolescents[5] (roughly 11-19 years of age). According to the enclosed Somogyi report on consumption, that is approximately the amount of caffeine consumed by individuals between the ages of 14-21 (see Table 33, page 63). Others take a more conservative stand on this point. For example, the Institute of Medicine has expressed the opinion that stimulant-containing drinks and other products have no place in the diets of children or adolescents (IOM, 2007)[6] because of the risk of symptoms of physical dependence and withdrawal such as sleeplessness and irritability. Although there are limited studies on caffeine dependence and withdrawal in school age children, IOM considered that these effects may be similar in children as in adults.

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[2] FDA notes that Figure 11 of Somogyi 2010, which refers to Table 33, has erroneously reported lower figures than those in the Table.

[3] Nawrot, P., Jordan, S., Eastwood, J., Rotstein, J., Hugenholtz, A. and Feeley, M., 2003, Effects of caffeine on human health. *Food Additives and Contaminants*, 20(1), pp. 1-30.

[4] Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment. Statement on the Reproductive Effects of Caffeine. United Kingdom Food Standards Agency, November 4, 2008. (Accessed on October 9, 2012 at *http://cot.food.gov.uk/cotstatements/cotstatementsyrs/cotstatements2008/cot200804*.)

[5] FDA contacted the American Academy of Pediatrics (AAP) and reviewed its website and was unable to verify an AAP policy statement for the cited value of 100 mg caffeine/d as the upper limit of caffeine consumption for adolescents.

[6] Institute of Medicine. Nutrition Standards for Foods in Schools: Leading the Way Toward Healthier Youth. Washington, DC, National Academies Press, 2007.

FDA agrees that it may be advisable for certain subpopulations, including children and pregnant women, to limit their caffeine consumption and will discuss this with relevant health professional groups.

FDA Regulation of Caffeine Levels in "Energy Drinks"

Finally, you urged FDA to assert its authority to regulate the level of caffeine in "energy drinks." As noted earlier in this letter, we are committed to addressing the issues you have raised and taking science-based actions needed to protect public health, within the bounds of our statutory authority and mandate. Depending on the outcome of our on-going review of the safety of "energy drinks," which includes caffeine alone and in combination with other ingredients, we will take action as needed with respect to the levels of caffeine in these products. In addition, based on our safety review and within the bounds of our authority, FDA will consider taking appropriate action with respect to the labeling of these products, such as requiring disclosure of the amount of caffeine in food products, limitations on intended use, or warnings about possible adverse effects.

Thank you, again, for your interest in this matter. If you have any further questions or concerns, please let us know. The same letter has been sent to Senator Blumenthal.

Sincerely,

for Michele Mital
Acting Associate Commissioner
for Legislation

Enclosure