

Highly Concentrated Caffeine in Dietary Supplements: Guidance for Industry

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**U.S. Department of Health and Human Services
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Highly Concentrated Caffeine in Dietary Supplements: Guidance for Industry¹

This guidance represents the current thinking of the Food and Drug Administration (FDA or we) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA staff responsible for this guidance as listed on the title page.

I. Introduction

Products consisting of or containing only pure or highly concentrated caffeine have been linked to at least two deaths in the United States in the last few years, and continue to present a significant public health threat. Many products that consist of only or primarily pure or highly concentrated caffeine are sold as dietary supplements. FDA considers some such products to be adulterated under section 402(f)(1)(A) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) [21 U.S.C. § 342(f)(1)(A)], because they are dietary supplements that present a significant or unreasonable risk of illness or injury under the conditions of use recommended or suggested in the labeling or, if no conditions for use are suggested or recommended, under ordinary conditions of use.

This document is intended to provide guidance to firms that manufacture, market, or distribute dietary supplement products that contain pure or highly concentrated caffeine, or are considering doing so. This guidance should help such parties determine whether their products are or would be adulterated under section 402(f)(1)(A) of the FD&C Act.

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe our current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited.

¹ This guidance has been prepared by the Office of Dietary Supplement Programs in the Center for Food Safety and Applied Nutrition (CFSAN) at the Food and Drug Administration.

The use of the word *should* in FDA guidances means that something is suggested or recommended, but not required.

II. Background

Caffeine (1, 3, 7-trimethylxanthine) is a naturally-occurring member of the methylxanthine class of compounds (Ref 1). Even though it is not an essential nutrient, caffeine is one of the most commonly consumed stimulants world-wide due to its abundant presence in food products, as well as over-the-counter and prescription drugs. While caffeine content varies in different products, a typical eight-ounce cup of ground coffee contains approximately 95 milligrams (mg) of caffeine.

Caffeine is rapidly absorbed into the bloodstream after ingestion, reaching peak serum concentration in less than two hours (Ref 4, 7, 8, 9, 10, 11). Its metabolism is slowed after consumption of more than 500 mg, leading to symptoms being experienced for an extended period of time (Ref 8, 12, 13). In short, this means that when an individual consumes a high dose of caffeine, he or she will experience the effects quickly and for a longer period of time. Toxic effects (including tachycardia, ventricular arrhythmia, and seizures) are observed at approximately 1200 mg, or 1.2 grams (0.15 tablespoons of caffeine) (Ref 2, 3, 4, 5, 6). A life-threatening dose of caffeine is typically estimated at between 10,000 and 14,000 mg, or 10 and 14 grams (g) (1.2 – 1.7 tablespoons of caffeine), although smaller doses can be life-threatening in certain individuals (such as children or other sensitive populations) (Ref 5, 14, 15, 16, 17).

In recent years, dietary supplement products containing pure or highly concentrated caffeine in powder or liquid forms have been increasingly marketed to consumers, often through online retailers. These products are often marketed in bulk packaging with up to thousands of servings per container, requiring the consumer to measure out a safe serving (often estimated at 1/16 of a teaspoon or less for powdered products) from what can be a toxic or even lethal amount of bulk product. For example, just one teaspoon of a powdered pure caffeine product can contain approximately 3200 mg (or 3.2 g) of caffeine, or the equivalent of 28 cups of coffee – in other words, two and a half times a toxic dose. And a half cup of a representative liquid concentrated caffeine product contains approximately 2,000 mg of caffeine, which is the equivalent to more than twenty typical cups of coffee and is well more than a toxic dose. Many of these products can present a significant or unreasonable risk of illness or injury.

III. Product Types

A. Powdered Dietary Supplements Containing Highly Concentrated Caffeine

One product type that has appeared on the market in recent years is powdered caffeine-containing products labeled as dietary supplements. FDA has issued warning letters to

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manufacturers of some of these products based on our finding that the products are adulterated.^{2,3,4,5,6}

Pure or highly concentrated powdered caffeine is often sold in packages containing enough powder for thousands of recommended servings. Large or “bulk” packages like these contain hundreds of potentially lethal doses.

The package labeling for these products often includes directions suggesting that a consumer consume 50 to 200 mg of caffeine multiple times daily. To obtain quantities such as these from a bulk container, a consumer must be able to accurately and precisely measure out a recommended serving in the range of 1/64 of a teaspoon (50 mg of powder) to 1/16 of a teaspoon (200 mg of powder). While we do not rule out the possibility that a powdered caffeine product sold in bulk could be permissible under the FD&C Act (for example, if it were sufficiently diluted), in general we consider these types of products – i.e., products containing amounts of pure or highly concentrated powdered caffeine that could be toxic or even lethal several times over, sold in bulk such that the consumer is required to separate out a safe serving from a potentially lethal amount – to meet the standard for adulteration under section 402(f)(1)(A) of the FD&C Act. Under section 301(a) of the FD&C Act [21 U.S.C. § 331(a)], adulterated products may not be introduced or delivered for introduction into interstate commerce.

Some of the pure or highly concentrated powdered caffeine products bear warning statements on their package labeling and/or websites. However, FDA considers many of these products to be sufficiently dangerous such that a warning cannot remedy the adulteration. Bulk powdered caffeine products are sold to consumers in packages as large as 10 kilograms, which contains the equivalent to more than 10,000 recommended servings of the product. A bulk product of that size contains hundreds of potentially lethal doses. For a number of reasons, no warning statement on the labeling of these products is adequate to prevent the products from being adulterated under section 402(f)(1)(A) of the FD&C Act.

Through surveillance we have observed discussions and comments on caffeine product websites and other fora indicating that these products are frequently shared by or dispensed to multiple users, increasing the risk of the product being separated from the warning statement. In many cases there is enough product in the package to last for years beyond the labeled expiration date, unless the product is shared among multiple consumers.

⁴ <https://www.fda.gov/ICECI/EnforcementActions/WarningLetters/2015/ucm460201.htm>

⁵ <https://www.fda.gov/ICECI/EnforcementActions/WarningLetters/2015/ucm460204.htm>

⁶ <https://www.fda.gov/ICECI/EnforcementActions/WarningLetters/2015/ucm460208.htm>

⁷ <https://www.fda.gov/ICECI/EnforcementActions/WarningLetters/2015/ucm460200.htm>

⁸ <https://www.fda.gov/ICECI/EnforcementActions/WarningLetters/2015/ucm460203.htm>

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Additionally, some consumers who are familiar with caffeine and have not encountered safety problems when consuming it in other ways (e.g., in coffee or soft drinks), might incorrectly assume they are personally able to disregard a warning statement and safely consume the product without careful attention to the precise serving and measurement recommendations. The volume of the product available and the labeled expiration date (which, taken together, could imply that a single consumer can finish the product before it expires) might further promote the misconception that the warning can be disregarded.

The serving size measurement can also limit the effectiveness of any warning statement. Some products specify that a serving is a non-standard measure, such as 1/16 of a teaspoon (the smallest standard kitchen measuring spoon is usually 1/4 teaspoon) or 200 mg (most household scales measure in kilograms and grams, not milligrams). Because consumers are unlikely to have the correct tools to accurately measure these amounts, even a consumer who reads the warning statement and attempts to measure a safe serving might inadvertently consume an unsafe amount. A simple mistake, such as measuring a serving in grams rather than milligrams, could result in a toxic dose being consumed.

Some pure or highly concentrated powdered caffeine products are packaged with tiny measuring scoops that purport to measure a single serving. However, FDA still considers many of these products to be adulterated. As discussed above, we are aware that these products are frequently shared among multiple users. If the product is physically divided up to be shared by multiple people living separately, some consumers will not have the benefit of the measuring scoop.

Furthermore, reasonably foreseeable measurement errors, such as packing the powder too tightly or use of a “heaping scoop” instead of a “level scoop,” can increase the amount of caffeine in a single dose by more than 200%, resulting in the ingestion of a toxic quantity of caffeine. These scoops can also easily be lost, in which case consumers might substitute common household measuring tools or even just regular spoons without realizing the possible impact.

For these reasons, in general we consider products containing potentially lethal amounts of pure or highly concentrated powdered caffeine, sold in bulk such that the consumer is required to separate out a safe serving from a potentially lethal amount, to meet the standard for adulteration under section 402(f)(1)(A) of the FD&C Act. Even if the product label specifies a serving size that could be considered safe for many healthy adult consumers, a scoop is provided that can approximate that serving size, and a warning statement urges the consumer not to exceed the serving size, this type of product can still present a significant or unreasonable risk of illness or injury under the conditions of use recommended or suggested in the labeling. An inherent feature of the conditions of use for such products is that the consumer must separate out a very small, precise serving from a potentially lethal amount of product – a task that poses a significant or unreasonable risk of illness or injury.

B. Liquid Dietary Supplements Containing Highly Concentrated Caffeine

We have also begun to see liquid products containing highly concentrated caffeine that are labeled as dietary supplements. These products are often sold in containers holding enough liquid for hundreds of recommended servings. As with the powdered bulk caffeine products, large or “bulk” containers of liquid like these contain multiple toxic or potentially lethal doses. While we do not rule out the possibility that a liquid dietary supplement product containing highly concentrated caffeine, sold in bulk, could be permissible under the FD&C Act (for example, if its concentration were sufficiently low), in general, we consider the types of products described here – i.e., products containing amounts of highly concentrated liquid caffeine that could be toxic or even lethal several times over, sold in bulk such that the consumer is required to separate out a safe serving from a potentially lethal amount – to meet the standard for adulteration under section 402(f)(1)(A) of the FD&C Act. Under section 301(a) of the FD&C Act, adulterated products may not be introduced or delivered for introduction into interstate commerce.

The package labeling for these highly concentrated liquid caffeine products often includes directions suggesting that a consumer consume one teaspoon, which is equivalent to approximately 80 mg of caffeine. These products are often sold to consumers in packages as large as a gallon, which contains the equivalent of more than 750 recommended servings of the product. A product of that size contains multiple potentially lethal doses.

These products are typically meant to be diluted before being consumed, and not consumed “as is.” An amount of highly concentrated liquid caffeine that would be safe for a given individual to consume in a properly diluted solution could nonetheless be unsafe for the same individual if the highly concentrated liquid were consumed directly. In the reasonably foreseeable scenario where a consumer makes an error diluting the product, or does not dilute it at all, that consumer could ingest a toxic quantity of caffeine. For example, a consumer who pours a representative liquid product from its bulk container into an empty container from a commonly-available single serving “energy shot,” would consume approximately five times the amount of caffeine contained in the original product – a potentially toxic amount.

Some highly concentrated liquid caffeine products bear warning statements on their package labeling and/or websites. However, FDA considers many of these products to be sufficiently dangerous such that a warning cannot remedy the adulteration. The high concentration of these products is such that reasonably foreseeable measurement errors, such as using a tablespoon instead of a teaspoon, could result in consumption of a toxic amount. Moreover, because many consumers are familiar with caffeine and have not encountered safety problems when consuming it in other ways, often as a beverage (e.g., in coffee or soft drinks), consumers might incorrectly assume that they are personally able to disregard a warning statement and safely consume the product without diluting it properly, or without careful attention to the precise measurement and serving recommendations.

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Additionally, similar to their powdered counterparts, highly concentrated liquid caffeine products are often sold in containers so large that they contain enough recommended serving sizes to last beyond the labeled expiration date, which suggests that the products are meant to be consumed by multiple users. It is reasonable to infer that liquid dietary supplements containing highly concentrated caffeine are being shared by or dispensed to multiple users, thereby increasing the risk of the product being separated from the warning statement and the directions for use.

Some highly concentrated liquid caffeine products are packaged with measuring devices that purport to measure a single serving. However, FDA still considers many of these products to be adulterated. These measuring devices are typically not accurate enough to prevent measurement errors, such as accidentally overpouring the liquid caffeine product, that can increase the amount of caffeine in a single dose, resulting in the ingestion of a toxic quantity of caffeine. Also, as discussed above, consumers who frequently consume caffeine in other contexts (e.g., in coffee or soft drinks) might incorrectly assume that they are personally able to exceed the serving size recommendation, without understanding the extent to which even a small dose of these highly concentrated products can be toxic or even lethal.

Furthermore, these products are often sold as clear liquids that could be relatively easily confused with commonly-available safe, clear liquids (e.g., water or white vinegar). A consumer could mistakenly confuse one of these products with water and quickly ingest enough highly concentrated liquid caffeine to cause toxic or even lethal consequences. Some highly concentrated liquid caffeine products are sweetened with a flavoring agent, which could increase the likelihood that a consumer would quickly ingest a toxic or even lethal amount.

For these reasons, in general we consider products containing potentially lethal amounts of highly concentrated, liquid caffeine, sold in bulk such that the consumer is required to separate out a safe serving from a potentially lethal amount, to meet the standard for adulteration under section 402(f)(1)(A) of the FD&C Act. Even if the product label specifies a serving size that could be considered safe for many healthy adult consumers, a measuring device is provided that can approximate that serving size, and a warning statement urges the consumer not to exceed that serving size, this type of product can still present a significant or unreasonable risk of illness or injury under the conditions of use recommended or suggested in the labeling. An inherent feature of the conditions of use for such products is that the consumer must separate out a small, precise serving from a potentially lethal amount of product – a task that poses a significant or unreasonable risk of illness or injury.

IV. Guidance on Producing Safer Dietary Supplements Containing Caffeine

When formulated and marketed appropriately, caffeine can be an ingredient in a dietary supplement that does not present a significant or unreasonable risk of illness or injury.

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Assuming that the product otherwise complies with all applicable legal requirements, we do not expect to consider the following types of dietary supplements to be adulterated:

- A. Dietary supplements sold in solid dosage forms, such as tablets or capsules that do not provide an excessive amount of caffeine per item. Products in these forms eliminate the need for a consumer to accurately measure the appropriate serving.
- B. Dietary supplements containing powdered or liquid caffeine (either diluted or undiluted) that are sold in premeasured packets or containers, with each premeasured unit containing an amount of caffeine that is not excessive. Products that are sold in pre-measured quantities eliminate the need for a consumer to measure the appropriate amount.
- C. Bulk powdered or liquid caffeine dietary supplement products that have been significantly diluted to low enough concentrations of caffeine, such that a reasonably foreseeable measurement error, misreading of the directions, or misunderstanding about the nature of the product would not normally be expected to lead to toxic or life-threatening symptoms.

All dietary supplements are required to comply with the adulteration provisions of the FD&C Act, and we intend to carefully review any dietary supplement products that contain potentially dangerous amounts of caffeine in any form.

V. References

- Ref. 1. Artin B, Singh M, Richeh C, Jawad E, Arora R, Khosla S. 2010. Caffeine-related atrial fibrillation *Am J Ther* 17: e169-171.
- Ref. 2. Bonsignore A, Sblano S, Pozzi F, Ventura F, Dell'Erba A, Palmiere C. 2014. A case of suicide by ingestion of caffeine. *Forensic Sci Med Pathol* 10 :448-451.
- Ref. 3. Holmgren P, Norden-Pettersson L, Ahlner J. 2004. Caffeine fatalities--four case reports. *Forensic Sci Int* 13971-73.
- Ref. 4. Jabbar SBH, M.G. 2013. Fatal caffeine overdose: A case report and review of literature. *American Journal of Forensic Medicine and Pathology* 34: 321-324.
- Ref. 5. Bannerjee PA, Z.; Levine, B.; Fowler, D.R. 2014. Fatal caffeine intoxication: A series of eight cases from 1999 to 2009. *Journal of Forensic Sciences* 59: 865-868.
- Ref. 6. Riesselmann BR, F.; Roscher, S.; Schneider, V. 1999. Fatal caffeine intoxication. *Forensic Science International* 103: S49-S52.
- Ref. 7. Nawrot P, Jordan S, Eastwood J, Rotstein J, Hugenholtz A, Feeley M. 2003. Effects of caffeine on human health. *Food Addit Contam* 20: 1-30.
- Ref. 8. Kaplan GB, Greenblatt DJ, Ehrenberg BL, Goddard JE, Cotreau MM, Harmatz JS, Shader RI. 1997. Dose-dependent pharmacokinetics and psychomotor effects of caffeine in humans. *J Clin Pharmacol* 37: 693-703.

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- Ref. 9. Fredholm BB, Battig K, Holmen J, Nehlig A, Zvartau EE. 1999. Actions of caffeine in the brain with special reference to factors that contribute to its widespread use. *Pharmacol Rev* 51: 83-133.
- Ref. 10. Mandel HG. 2002. Update on caffeine consumption, disposition and action. *Food and Chemical Toxicology* 40: 1231-1234.
- Ref. 11. Zulli AS, R.M.; Kubatka, P.; Novak, J.; Uehara, Y.; Loftus, H.; Qaradakhi, T.; Pohanka, M.; Kobyliak, N.; Zagatina, A.; Klimas, J.; Hayes, A.; La Rocca, G.; Soucek, M.; Kruzliak, P. 2016. Caffeine and cardiovascular diseases: Critical review of current research. *European Journal of Nutrition* 55: 1331-1343.
- Ref. 12. Dalvi RR. 1986. Acute and chronic toxicity of caffeine: A review. *Vet Hum Toxicol* 28: 144-150.
- Ref. 13. Magkos FK, S.A. 2006. Caffeine use in sports, pharmacokinetics in man, and cellular mechanisms of action. *Critical Reviews in Food Science and Nutrition* 45:535-562.
- Ref. 14. Shum S, Seale C, Hathaway D, Chucovich V, Beard D. 1997. Acute caffeine ingestion fatalities: management issues. *Vet Hum Toxicol* 39: 228-230.
- Ref. 15. Thelander G, Jonsson AK, Personne M, Forsberg GS, Lundqvist KM, Ahlner J. 2010. Caffeine fatalities--do sales restrictions prevent intentional intoxications? *Clin Toxicol (Phila)*,48: 354-358.
- Ref. 16. Laskowski LK, Henesch JA, Nelson LS, Hoffman RS, Smith SW. 2015. Start me up! Recurrent ventricular tachydysrhythmias following intentional concentrated caffeine ingestion. *Clin Toxicol (Phila)* 53: 830-833.
- Ref. 17. Ammar R, Song JC, Kluger J, White CM. 2001. Evaluation of electrocardiographic and hemodynamic effects of caffeine with acute dosing in healthy volunteers. *Pharmacotherapy* 21: 437-442.