Memorandum

Date	November 16, 2015
From	, Ph.D. Toxicology Reviewer, HFS-255 Division of Biotechnology and GRAS Notice Review (DBGNR) Office of Food Additive Safety (OFAS) Center for Food Safety and Applied Nutrition (CFSAN) Through , Ph.D. Toxicology Supervisor, HFS-255
Subject	Regulatory status and review of available information pertaining to picamilon (N-nicotinoyl-γ-aminobutyric acid): Lack of information on the safety and general recognition of safety for its use in conventional food.
To	, Ph.D. Division Director, DBGNR, HFS-255

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GRAS Provision in Defining a Food Additive

As defined in section 201(s) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) [21 U.S.C. § 321(s)], the term "food additive" refers to any substance the intended use of which results in it becoming a component of any food, unless the substance is the subject of a prior sanction or is generally recognized as safe (GRAS) among qualified experts under the conditions of its intended use. Furthermore, under section 201(s) of the FD&C Act, a substance is exempt from the definition of a food additive and thus, from premarket approval requirements, if its safety is generally recognized by qualified experts.

As there is no food additive regulation establishing safe conditions of use of picamilon as an ingredient in food, this memorandum will consider the applicability of the GRAS criteria for the use of picamilon as an ingredient in food.

The GRAS Standard

A determination that the intended use of a substance is GRAS requires that the information about the substance satisfies two criteria: (1) that the substance be safe to consume under the proposed conditions of use (technical evidence of safety) and (2) that this evidence of safety be generally known and accepted (general recognition of safety).

Technical Evidence of Safety: Under 21CFR§170.30(a)-(c), general recognition of safety must be based on the views of experts qualified by scientific training and experience to evaluate the safety of substances directly or indirectly added to food. The basis of such views may be either (1) scientific procedures or (2) in the case of a substance used in food prior to January 1, 1958, through experience based on common use in food. The technical evidence of safety established through scientific procedure involves generation of data and information through various studies, such as toxicological and metabolism studies, to name a few. FDA has defined "safe" (21CFR§170.3(i)) as a reasonable certainty in the minds of competent scientists that the substance is not harmful under its intended conditions of use.

General recognition of safety: The general recognition of safety standard associated with a GRAS determination includes two facets: (1) the data and information relied on as evidence of safe use in food must be generally available; and (2) there must be a basis to conclude that there is consensus among qualified experts about the safety of the substance for its intended use in food. The usual mechanism to establish that scientific information is generally available is to show that the information is published, such as in a text or reference book, or in a peer-reviewed scientific journal. Mechanisms to establish the basis for concluding that there is expert consensus about the safety of a substance are more varied. Most often, publication in a peer-reviewed scientific journal of data on a test substance has been used to establish expert consensus in addition to general availability (62 FR 18938; April 17, 1997; Substances Generally Recognized as Safe (GRAS); the GRAS proposal).

FDA's regulations in 21CFR§170 define "common use in food" and establish eligibility criteria for classification as GRAS through experience based on common use in food. Under 21CFR§170.3(f), common use in food means "a substantial history of consumption of a substance for food use by a significant number of consumers."

Similarly, FDA's regulations in 21CFR§170 define "scientific procedures" and establish eligibility criteria for classification as GRAS through scientific procedures. Under 21CFR§170.3(h), scientific procedures "include those human, animal, analytical, and other scientific studies, whether published or unpublished, appropriate to establish the safety of a substance." Under 21CFR§170.30(b), general recognition of safety based upon scientific procedures "shall require the same quantity and quality of scientific evidence as is required to obtain approval of a food additive regulation for the ingredient." Section 170.30(b) further states that general recognition of safety through scientific procedures is ordinarily based upon published studies, which may be corroborated by unpublished studies and other data and information.

Overview of Picamilon

Picamilon (N-nicotinoyl-γ-aminobutyric acid) is a chemically synthesized drug that combines nicotinic acid (niacin) and γ-aminobutyric acid (GABA). Nicotinic acid serves as a precursor to coenzymes NAD/NADP but also has vasodilatory and hypolipidemic properties. GABA is a neurotransmitter that has both inhibitory and stimulatory effects depending on developmental age and target site. Because GABA does not appreciably cross the blood-brain barrier (BBB) in the adult, GABA esters and other GABA-mimetics have been formulated to treat neurological diseases linked to low bioavailability of GABA in the brain. The nicotinoyl moiety allows GABA to cross the BBB much more readily compared to GABA itself. Once in the brain, picamilon is thought to be hydrolyzed to nicotinic acid and GABA, although this has not been firmly established (Goldberg 2010; Matsuyama et al. 1984). Thus, picamilon, if it is hydrolyzed, may have biological activities of both nicotinic acid and GABA, while the parent compound itself, if not hydrolyzed, may have complex unknown effects in the central nervous system (CNS).

Regulatory Status of Picamilon

There is no evidence from the literature searches that picamilon has been used in conventional foods. Niacin is GRAS (21CFR§184.1530) as a direct human food ingredient at current Good Manufacturing Practice levels.

In Russia, picamilon has prescribed uses as a drug[1] to treat a variety of ailments including migraine headaches, urinary problems, anxiety, and other neurological problems. In the United States, Canada, Australia and Europe, picamilon is not approved as a drug, although GABA-mimetic drugs (such as gabapentin and pregabalin)[2] have been approved in the United States for use in management of seizure disorders, neuropathic pain, and fibromyalgia. GABA (trade name "Gammalon"; KEGG Drug Database entry D00058), but not picamilon, is listed as a drug sold in Japan. Although no clinical studies for picamilon are listed in the National Institutes of Health clinical trials database[3], clinical trials have been described for picamilon in Russian and Ukrainian publications (Kruglikova-L'vova et al. 1989).

FDA is unaware of picamilon's use in conventional foods prior to 1958. Thus it does not meet the "common use in food" criterion. Therefore, its eligibility for classification as GRAS needs to be established on the basis of "scientific procedures." This provision requires existence of adequate technical evidence of safety under the conditions of intended use in conventional food, and such evidence of safety has to be generally recognized and accepted by qualified experts in the field.

A literature search in the PubMed in November of 2015 using the search terms "picamilon OR pikamilon OR pykamilon" under default settings retrieved 54 articles, of which only 5 were either written in or fully translated into English, 44 were written in Russian, and 5 were written in Ukrainian. Based on the English translations of the titles and abstracts for the publications written in Russian or Ukrainian, those studies were deemed not relevant to a safety assessment of picamilon in conventional food use because those studies focused on safety of picamilon as a drug. A review (Kruglikova-L'vova et al. 1989), originally written in Russian but translated into English, was found as one of the cited references from the retrieved searches. This review article appeared to summarize much of the toxicological and absorption/distribution/metabolism/elimination (ADME) studies that were previously published in Russian without citing specific reference(s) for its summarization. As such, the accuracy and reliability of the review could not be assessed, and this publication was not used for safety assessment. Regardless, the other available scientific information indicates that the use of picamilon in food is a cause for concern.

Lack of Sufficient Data to Establish Safety in Conventional Food Use

Given the structure of picamilon, it may possess properties of both nicotinic acid and GABA. Whether the combined pharmacologic effects of nicotinic acid and GABA (for example, vasodilatory effects by nicotinic acid and neural depressant and/or hypotensive effects by GABA) have the potential to lead to broader complex systemic effects upon chronic exposure is not known.

Nicotinic acid has well-known adverse effects, such as skin toxicity (i.e., flushing and itching), gastrointestinal (GI) effects (i.e., diarrhea, nausea, and constipation), and hepatotoxicity, that significantly restrict its therapeutic potential (Dunbar and Gelfand 2010; Kei, Liberopoulos, and Elisaf 2011; Lloyd-Jones 2014). "Flushing" or rubor[4] was seen in some human subjects at doses as low as 30 milligrams (mg) per day (Sebrell and Butler 1938), whereas higher doses are associated with other adverse effects such as GI effects (>1000 mg/day) and hepatotoxicity (>500 mg/day) (SCF 2002). Whether or not these adverse effects are of safety concern for picamilon added to conventional food would depend on the expected exposure that results from specified use levels in defined categories of food. The Scientific Committee on Food of the European Union has set a Tolerable Upper Intake Level (UL) for nicotinic acid at 2-8 mg/day for children 1-18 years of age and 10

[1] According to Kruglikova-L'vova et al. (1989), picamilon was approved as a drug by the Ministry of Health of the USSR (Registration No. 86/1642/5).

[2] Other examples include ß-(4-chlorophenyl)-γ-aminobutyric acid (Baclofen), 4-[4-Chlorophenyl)-(5-fluoro-2-hydroxy-phenyl)-methylidene] aminobutanamide (Progabide), and 4-amino-3-hydroxygutanoic acid (GABOB).

[3] https://clinicaltrials.gov/ accessed November 3, 2015.

[4] Although " flushing" or rubor is often used in the literature to describe the general nicotinic acid-induced skin irritations, Dunbar and Gelfand (2010) instead propose the use of the term "niacin-associated skin toxicity" which include flushing/rubor, itching, calor, and dolor. Flushing is not associated with nicotinamide.

mg/day for adults (SCF 2002). The National Academies' Institute of Medicine has set its UL for niacin (including both nicotinic acid and nicotinamide) at 35 mg/day for adults and 10-30 mg/day for children 1-18 years of age (IOM 1998). For both determinations, short-term flushing by nicotinic acid was used as the Lowest Observed Adverse Effect Level (30-50 mg/day). More life-threatening adverse effects such as hepatotoxicity were observed at doses an order of magnitude or greater than the LOAEL[5].

Interestingly, the types of observed adverse effects may be influenced by the use of different formulations of nicotinic acid. Currently, nicotinic acid is available as "immediate-release" (IR), "extended-release" (ER), or "sustained-release" (SR), with ER showing dissolution kinetics in between that of IR and SR (Pieper 2002). The incidence of flushing, but not hepatotoxicity, is lowered with SR formulations, whereas hepatotoxicity is not observed with IR formulations (McKenney et al. 1994; Pieper 2002; SCF 2002). It has been suggested that ER formulation best minimizes the combined adverse effects compared to IR and SR formulations (Alsheikh-Ali and Karas 2008; Pieper 2002). These observations suggest that potential adverse effects from low but chronic exposure of the nicotinic moiety of picamilon would be difficult to predict without extensive ADME studies of picamilon. Furthermore, the effects of food matrices in absorption and metabolism of foods containing picamilon would need to be explored experimentally.

Picamilon was originally designed as a GABA-mimetic drug, possessing the same biological activities of GABA but having the ability to more easily cross the BBB compared to GABA (Kopelevich, Sytinskii, and Gunar 1981). As such, safety concerns for GABA become accentuated for picamilon, given its ability to cross the BBB more readily. Although potential adverse effects of GABA in food use have not been well investigated, the following points raise concerns:

- Because GABA switches from depolarizing (stimulatory) to hyperpolarizing (inhibitory) during gestation, GABA has an important role in neuronal growth and synapse formation during fetal/neonatal stages (Ben-Ari 2002; Owens and Kriegstein 2002). Since there is no reason to suspect picamilon would not cross the placental barrier or not become components of breast milk (Limon et al. 2014), picamilon could potentially affect fetal and neonatal brain development.

- GABA has an important role in the hypothalamus-pituitary axis during sexual maturation during puberty as well as reproductive cycles in adults by modulating gonadotropin releasing hormone (Maffucci and Gore 2009).

- GABA and GABA agonists have been shown to affect pituitary/hypothalamic function by modulating growth hormone and prolactin release (Kreft and Zorec 2008; Powers 2012; Tamminga et al. 1978; Willoughby et al. 1986; Cavagnini et al. 1980).

- Several known adverse effects of GABA agonist drugs must also be considered. For example, ß-(4-chlorophenyl)-γ-aminobutyric acid (commonly referred as Baclofen) has been reported to have adverse effects during pregnancy (Anonymous 2015; Moran et al. 2004).

- Long-term feeding studies, as well as developmental and reproductive toxicity studies, are lacking for both picamilon and GABA.

Thus, the use of picamilon in conventional food would raise safety concerns with respect to fetal/neonatal brain development as well as effects on the hypothalamus/pituitary axis, which could result in adverse effects in pregnancy, lactation, reproduction, and development.

[5] Differences in UL recommendations are partly due to differences in the "uncertainty factor" used (1.5 for IOM and 3 for SCF).

Section 301(ll) of the FD&C Act

Section 301(ll) of the FD&C Act prohibits the introduction or delivery for introduction into interstate commerce of any food that contains a drug approved under section 505 of the FD&C Act, a biological product for which substantial clinical investigations have been instituted and their existence made public, unless one of the exemptions under section 301(ll)(1) – (4) applies. At this time FDA has not made any determination regarding whether 301(ll) or any of its exemptions apply to foods containing picamilon.

Conclusions

GRAS exemption requires not only the safety of the intended use of that substance but also such safety is generally recognized by experts qualified by scientific training and experience to evaluate the safety of substances added to food. A safety determination for a substance that will be used as an ingredient in conventional food must be based on scientific studies appropriate to establish the safety of the substance under the conditions of its intended use. It should be emphasized that, because a food ingredient in a conventional food may be consumed by the entire population over a lifetime, assurance of safety requires an evaluation of potential effects of long-term use. Review of the current literature on GABA as well as on picamilon revealed that there are not sufficient data for evaluating their safety for use as food ingredients. Based on the English translations of the titles and abstracts, publications in Russian or Ukrainian were deemed not relevant to a safety assessment of picamilon in conventional food use because those studies focused on safety of picamilon as a drug. Therefore, a safe level of consumption in food below which there would be no effects cannot be assumed or established without additional studies. Analyses of the available literature indicate that the technical evidence to support the safety standard associated with a GRAS determination is lacking for picamilon. For the use of picamilon as an ingredient in food, FDA considers that the available scientific information as described above raise safety concerns about the use of the substance. In light of these safety concerns, there is no basis to conclude that the use of picamilon as an ingredient in conventional food is generally recognized as safe (GRAS). Moreover, there is no food additive regulation in effect establishing safe conditions of use of picamilon, and FDA is not aware of any information to indicate that picamilon is the subject of a prior sanction. Therefore, FDA considers picamilon an unapproved food additive when used as an ingredient in conventional food.

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