May 15, 2018

Dockets Management (HFA-305)
Food and Drug Administration (FDA)
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Re: *Best Practices for Convening a GRAS Panel: Guidance for Industry, Draft Guidance, Docket No. FDA-2017-D-0085*

The Center for Science in the Public Interest (CSPI), Consumer Federation of America (CFA), Environmental Defense Fund (EDF), respectfully submit the following comments regarding FDA's "Best Practices for Convening a GRAS Panel" draft guidance. The draft guidance is intended to reduce bias, minimize conflicts of interest and "appearance issues," ensure balance, and otherwise improve the credibility, reliability, and transparency of panels used in making determinations that an ingredient is "generally recognized as safe" (GRAS).

CSPI is a consumer group that has advocated for a healthier food system since 1971. CFA is an association of more than 250 non-profit consumer organizations that was established in 1968 to advance the consumer interest through research, advocacy and education. EDF is an environmental organization working to protect American families by strengthening and defending policies and advocating for greater corporate responsibility.

Our comments address the following three points:

I. The notion that GRAS panels convened by proponents are independent and can act as credible, representative, unbiased proxies for the larger scientific community is inherently and fundamentally flawed, and this guidance does not resolve that problem.

II. Evidence indicates that bias and conflicts of interest are rampant in the GRAS determination process, and that bias improperly affects the outcomes.

III. The recommendations in FDA's draft Best Practices Guidance for Convening a GRAS Panel would improve the integrity of GRAS panels insofar as they are followed, although additional steps are needed.

Overall, the FDA's draft Best Practices for Convening a GRAS Panel Guidance is best understood as an attempt to put a Band-aid over a compound fracture. While well-intentioned and grounded in the science of bias and conflicts of interest, without changes to FDA's separated final rule on GRAS, it will likely have little effect because GRAS safety determinations are currently made by those with a vested interest in a favorable outcome and lack appropriate public or FDA oversight. The stakes for such decisions are high: they concern both the safety of the

public and are a matter of acute financial interest to their proponent—typically, a company (or trade association) that is seeking to bring a new substance into the food marketplace.

Even in a well-designed system with proper safeguards and disclosure, research demonstrates that bias can affect decisions. Here, we lack such fundamental safeguards and will simply be unable to know whether the recommendations are being followed for any GRAS safety determinations made by industry in secret. Thus, FDA's mere assertion in this guidance of what would constitute best practices offers scant comfort, because they would be largely unenforceable.

Nonetheless, our comments consider the literature on bias and the agency's description of the practices followed by advisory and other scientific committees and offer our views on important ways to strengthen the FDA's guidelines, in hopes that someday GRAS safety determinations will be made in the light of public view and with appropriate FDA oversight, and that this exercise will therefore be of greater public health significance.

I. The notion that GRAS panels convened by proponents are independent and can act as credible, representative, unbiased proxies for the larger scientific community is inherently and fundamentally flawed, and this guidance does not resolve that problem.

An estimated 10,000 additives are currently used in food production, whether as a direct component or via indirect exposure such as in processing or packaging.[1] While some additives are government-approved, several thousand ingredients have been allowed to be added to food or food packaging through a loophole in federal law that allows companies to self-determine their safety without any government or public oversight.

A long-standing law, the Food Additives Amendment of 1958 (FAA), was intended by Congress to help ensure that new additives are safe for human consumption. Under the statute, all food additives must undergo a pre-market approval process by FDA to determine whether the anticipated use and application of the new additive is safe. Crucially, the term "food additive" excludes substances that are "generally recognized as safe" (or "GRAS").[2] An ingredient is GRAS if its condition of use is safe and the safety of that use is generally recognized by scientists knowledgeable about the safety of substances added to food.[3]

At the time the FAA was enacted, this exemption was intended to encompass familiar ingredients like oil and vinegar from the pre-market approval process. However, the scope of the GRAS exemption has since expanded to the point of absurdity. Under the current regulations, GRAS status (and eligibility for such status) is determined by *industry* without any required

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[1] Pew Charitable Trusts, Fixing the Oversight of Chemicals Added to Our Food, Nov. 2013: 1. (*Available online at* http://www.pewtrusts.org/en/research-and-analysis/reports/2013/11/07/fixing-the-oversight-of-chemicals-added-to-our-food.)

[2] 21 U.S.C. § 321(s).

[3] Thomas G. Neltner, Neesha R. Kulkarni, Heather M. Alger, Maricel V. Maffini, Erin D. Bongard, Neal D. Fortin, and Erik D. Olson, "Navigating the U.S. Food Additive Regulatory Program," *Comprehensive Reviews in Food Science and Food Safety* 10 (2011): 351. doi: 10.1111/j.1541-4337.2011. 00166.x.

oversight or input from FDA. If the industry decides that a use of a substance, however novel, is GRAS, it may be marketed for that use without agency review and approval. Unsurprisingly, this means that today virtually all new substances are allowed in food via the GRAS exemption rather than the food additive petition process (which would require pre-market review by FDA). The GRAS loophole has, over time and particularly since FDA's 1997 proposed rule weakening the system, "effectively swallowed the law."[4]

Because the industry is not currently required to seek approval from FDA regarding GRAS substances, FDA has concluded—wrongly—that the food industry is also not required to even *notify* FDA of new additives that it has determined to be GRAS. Of the roughly 10,000 additives currently used in food, an estimated 3,000 have not been reviewed by FDA.[5] Of these, 1,000 are self-affirmed as GRAS by additive manufacturers without notice to FDA, while another 2,000 are flavorings approved by an industry review process of which FDA is aware, but does not generally review or approve in any fashion.[6]

We note that this is a matter of public significance, as flaws in the current system obstruct FDA's ability to ensure the safety of additives in several respects. First, because industry uses the GRAS loophole to bypass its approval process, FDA can only address safety concerns related to these substances *after* they already entered the market, contrary to Congressional intent. Second, because industry is not required to even notify FDA of new GRAS safety determinations, FDA lacks information on ingredients in the food supply. FDA also does not know to what extent, or even whether, companies track evolving scientific information about substances they have determined to be GRAS. This makes it impractical at best for FDA to reassess the safety of existing GRAS substances or new food ingredients in light of changing science or exposure levels.

Because industry's GRAS safety determinations are essentially unregulated, firms routinely use their own employees, consultants, and experts to make safety decisions. Thus, bias and conflicts of interest among the additive manufacturers and the experts making the GRAS determinations are rampant. The current draft guidance represents FDA's attempt to address such problems. But, as an overarching matter, it is an absurd exercise for FDA to articulate guidance to alleviate bias and conflicts of interest on industry-run panels that lack FDA oversight—particularly those conducted in secret.[7]

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[4] Pew, *Fixing the Oversight*, 1.
[5] Neltner, *supra* note 3, at 355.
[6] Pew Charitable Trusts, *Fixing the Oversight*. The 2,000 flavors have been approved as GRAS by the industry trade group that approves flavors, the Flavor and Extract Manufacturers Association (FEMA). FDA has received only the most basic information concerning the safety of these substances but has not conducted any systematic review or approval of them. *Id.*
[7] *See generally* Substances Generally Recognized as Safe (GRAS), 62 Fed. Reg. 18938, FDA-1997-N-0020, Comments by Center for Science in the Public Interest (CSPI), Consumers Union, Environmental Working Group (EWG), and Natural Resources Defense Council (NRDC), April 15, 2015. (*Available online at:* https://cspinet.org/sites/default/files/attachment/GRAS%20Comment%20FINAL_0.pdf.)

While bias is obvious in the GRAS notices submitted to FDA,[8] it is a particular problem with regard to the secret GRAS process (industry self-determinations for which FDA receives no notification). Bias is both inescapable and undetectable in such a system. For these reasons, and to protect public safety, it is incumbent upon the agency to craft a system of oversight regarding the bias in secret GRAS self-determinations that does the most that it can do, given the industry's clear interests and its role as a source of funding for the determinations.

In 2010, the Government Accountability Office (GAO) issued a report calling on FDA to "[m]inimize the potential for conflicts of interest in companies' GRAS safety determinations, including taking steps such as issuing guidance for companies on conflict of interest *and requiring information in GRAS notices regarding expert panelists' independence*."[9] As GAO notes, guidance is insufficient by itself: the written and public disclosure aspects of the current draft guidance become all the more critical to any hope of mitigating bias.

Guidance alone is also patently insufficient as a legal matter. Under FDA policy and governing law, guidance merely states an agency's perspective in relation to its enforcement of statutory duties.[10] FDA's final rule on GRAS lacks any provision for oversight of industry's secret decisions on the GRAS status of an ingredient;[11] consequently, there can be no enforcement as to secret GRAS safety determinations.

It is also disappointing that FDA failed to include the recommendations in this non-binding guidance as requirements in the agency's final rule on GRAS determinations, as several commenters had requested in that docket.[12] Even after the rulemaking process on GRAS concluded, FDA could and should have published its draft principles on Best Practices for Convening a GRAS Panel as a second binding rule. These issues are central to the credibility of GRAS safety determinations and deserve treatment as such. For these reasons, we urge FDA to move this issue into rulemaking.

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[8] Thomas G. Neltner et al., *Conflicts of Interest in Approvals of Additives to Food Determined to Be Generally Recognized as Safe*, 173 JAMA Intern. Med. 2032, 2035 (2013). (*Available online at:* https://jamanetwork.com/journals/jamainternalmedicine/fullarticle/1725123.) [*Hereinafter:* "JAMA Study."]

[9] U.S. Government Accountability Office (GAO), *FDA Should Strengthen Its Oversight of Food Ingredients Determined to Be Generally Recognized as Safe (GRAS)*, GAO-10-246 21 (Feb. 2010), at 34 [*Emphasis added.*]. (*Available online at:* https://www.gao.gov/products/GAO-10-246).

[10] For example, FDA guidance typically includes the phrase "Contains Nonbinding Recommendations" in the header of each page.

[11] Substances Generally Recognized as Safe, Food and Drug Administration, Final rule, 81 FR 54960, Docket No. FDA–1997–N–0020, August 17, 2017.

[12] Comments to the agency's rule on GRAS noted, for example, that any GRAS notices should include information demonstrating the independence of experts who generate data or analysis underlying the GRAS finding. *See, e.g.*, Food & Water Watch, Comment on Docket No. FDA-1997-N-0020, Substances Generally Recognized as Safe; Reopening of the Comment Period (March 28, 2011), at 3; Michael Hansen, Comments of Consumers Union on Food and Drug Administration (FDA) Proposed rule on Substances Generally Recognized as Safe; Reopening Comment Period Docket No. FDA-1997-N-0020 (March 28, 2011), at 5.

We further recommend, as part of such a rule, that FDA require any company that conducts a GRAS safety determination to provide FDA and the public with documentation including critical information about the experts who participated in making the determination, their sources, and their findings, as well as compensation arrangements. In addition, FDA must establish an active role in monitoring and evaluating the sufficiency of steps taken to address conflicts of interest in GRAS safety determinations.

These steps are needed because the financial inter-dependencies require that protocols, findings and funding sources must be made available. As noted below, the literature on bias is clear and it shows that funding relationships, as well as professional affiliations and many other factors, can skew outcomes. As FDA's draft guidance notes, "[b]ias is a particular tendency, trend, inclination, feeling or opinion," and can be created both by cognitive patters and by factors such as the potential for financial gain."[13] FDA outlines its consequences: "The credibility of an opinion from a panel of scientific experts can be undermined if one or more members is, or is perceived to be, biased."[14] Because conflicts of interest are not a problem of "deliberate corruption, but of subconscious bias,"[15] the social science research suggests that a highly effective way to mitigate bias is to "realign incentives to eliminate conflicts."[16] For this reason, mechanisms that create functional independence for researchers in relation to their research outcomes—such as separate funding or independent oversight—are recommended.

Moreover, the bias in the current GRAS system—which utilizes a backroom set of industry consultants[17]—is far worse than is suggested by the body of research on bias, which generally measures bias in peer-reviewed, published study outcomes because that is what is publicly available for study. FDA therefore should develop, as part of a rule, objective measures that it could apply to monitor bias in GRAS safety determinations based on the principles in the draft guidance as well as the relevant literature, apply this system to monitor conflicts in GRAS safety determinations, assess the level of bias, and publish both its underlying data and conclusions in a public report.

Should adoption of a binding, mandatory regime of conflicts disclosure and substantive checks on conflicts prove to be insufficient to address bias in outcomes, based on such a measure, FDA must then develop a more proactive approach to preventing predictable bias, including conflicts of interest. Either through its existing regulatory authority or by soliciting

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[13] Best Practices for Convening a GRAS Panel: Draft Guidance for Industry, Food and Drug Administration, FDA-2017-D-0085, November 2017, at 8-9. [*Hereinafter*: "Draft Guidance"].
[14] *Id.* at 9.
[15] *Id.*
[16] *Id.*
[17] Elizabeth Weise, *Experts who decide on food additives conflicted*, USA Today, Aug. 18, 2013 (*available online at:* http://www.usatoday.com/story/news/nation/2013/08/07/food-additives-conflict-of-interest/2625211/):"The companies hire a consulting firm to get experts for them and then the experts review the information that's available and then they write a letter to FDA saying this additive should be considered GRAS," says Marion Nestle, a professor of nutrition at New York University. "There are whole companies that are in the business of recruiting scientists to sign off on these things," she says. "That was one of the amazing findings of this paper."

authority from Congress,[18] it should establish a group of credentialed and truly independent expert reviewers for GRAS notifications, funded by pooling industry user fees, and should base GRAS safety determinations on their reviews. *Ex parte* communication and funding between the pool of experts and the food industry could be barred, and *ad hoc* experts from the pool should be invited to participate as needed and appropriate. This is the gold standard for independence.

In sum, there is considerable doubt that any industry-funded process—however well monitored by FDA—could produce unbiased scientific determinations sufficient to assure public safety and create consumer confidence. What is also clear is that the contemplated guidance will fail to achieve FDA's mandate of assuring public safety, given the agency's inability to exercise oversight of conflict-ridden GRAS decisions.

II. Evidence indicates that bias and conflicts of interest are rampant in the GRAS determination process, and that bias improperly affects the outcomes.

A 2013 analysis in *JAMA Internal Medicine* provides the most recent, in-depth analysis of known conflicts in GRAS determinations.[19] Critically, the authors could analyze only those conflicts that pertained to then-available public GRAS notifications by industry to FDA. Although the review (and the public) lack any line of sight into *secret* GRAS determinations by industry, the authors nonetheless documented that conflicts in GRAS notifications were both common and widespread. One could infer that the conflicts or bias that afflict industry's secret GRAS decisions are likely to be far worse than those in notifications, as the latter are intended to be filed publicly with the agency.

The 2013 study reviewed industry's GRAS notifications between 1997 and 2012 and concluded that "financial conflicts of interest in these decisions are ubiquitous." [20] The research relied on criteria developed by the Institute of Medicine in 2009 that identified a framework to assess the severity of conflicts of interest.[21] Applying these standards to the 451 GRAS notices submitted to the FDA between 1997 and 2012, the researchers found that 22.4% were made by an employee of an additive manufacturer, 13.3% by an employee of a consulting firm selected by a manufacturer, and 64.3% by an expert panel selected by a manufacturer or a consultant to a manufacturer.[22] In *no* case did a manufacturer use a standing expert panel selected by an

[18] FDA has authority to accomplish this without the need for additional Congressional authorization because it has broad authorization to undertake activities needed to accomplish its overall mission. (FDA's rulemaking authority under Section 701(a) "has been broadly construed to uphold a wide variety of assertions of regulatory power" and is valid so long as it is reasonably related to an authorized regulatory objective. *See Pharm. Mfrs. Ass'n*, 484 F. Supp. at 1183; *see also U.S. v. Nova Scotia Food Products*, 568 F.2d 240, 246 (2d Cir. 1977) (finding that enforcement-related regulations are valid so long as they are reasonably related to the purposes of the enabling legislation).

[19] JAMA Study, *supra* note 8.

[20] *Id.* at E4.

[21] Institute of Medicine (US) Committee on Conflict of Interest in Medical Research, Education, and Practice, *Conflict of Interest in Medical Research, Education and Practice* (Bernard Lo & Marilyn Field, eds. 2009).

[22] JAMA Study, *supra* note 8, at E3-4.

independent third party—the method considered least likely to involve a conflict of interest short of FDA review.

When manufacturers convened an expert panel, the panels were small, typically only three people, all handpicked by the manufacturer or its hired consultant.[23] The researchers concluded that a manufacturer's employee would have the greatest likelihood of favoring a food substance as GRAS, while a member of a standing expert panel selected by an independent third party would be least likely to do so.

The researchers also found considerable overlap among the expert panels—at least 10 individuals served on 27 or more panels, while one person served on 128 panels (of the total 290 panels involved in GRAS determinations).[24] Thus, it is apparent that, even with notification, there are rampant and obvious conflicts of interest in GRAS determinations.

The Pew Charitable Trusts (Pew), with input from multiple reviewers and stakeholders in a public August 2013 workshop of experts, advocates and industry participants, also drafted guidance on avoiding conflicts of interest in GRAS evaluations and submitted it to the agency on September 4, 2013.[25] Relying in part on considerable FDA input, practices and documents, the report recommended that:

1) Conflicts of interest should be disclosed to FDA for its review; and
2) An expert should not be permitted to conduct a GRAS evaluation if he or she would be ineligible to serve on an FDA advisory committee without an agency waiver due to disqualifying financial interests.[26]

Since the FDA advisory committee guidance is primarily focused on financial factors, Pew identified several additional factors that should be considered, drawing from similar policies adopted by food industry groups and regulators.[27] The Pew draft notes that it "implements several of the U.S. GAO's recommendations from 2010 regarding the GRAS program."[28]

As part of a review process for Pew's draft guidance, its authors requested feedback from workshop participants and outside reviewers (all submitted to the docket along with the draft

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[23] *Id.*
[24] *Id.*
[25] The Pew Charitable Trusts, *Draft Guidance for Industry on Selection of Experts Conducting "Generally Recognized as Safe" (GRAS) Evaluations*, submitted to Docket No. FDA-1997-N-0020, Substances Generally Recognized as Safe; Reopening of the Comment Period (Sept. 4, 2013). [*Hereinafter*: "Pew Draft Guidance"]
[26] *Id.*, at 11-13.
[27] In particular, the Draft Guidance prompts the manufacturer or end user to answer 4 questions to evaluate whether the expert is qualified by scientific training and experience to evaluate whether a use of a food substance may qualify for the GRAS exemption and provides additional detailed guidance for evaluating responses for each question: 1) Does the expert have the necessary expertise? 2) Is the expert too close to the issue to objectively assess the consensus of the scientific community? 3) Is the expert disqualified because of serious financial conflicts of interest from exercising independent judgment? 4) Are there non-financial conflicts of interest that need to be considered? *Id.* at 9.
[28] *Id.* at 3.

guidance). Some of these reflections mirror the findings of the guidelines discussed below, including an observation that even small amounts of money or financial ties may unfairly influence decisions:[29]

> "A financial interest does not have to be great for the influence to be undue. Indeed, social science research suggests that gifts of small value may influence decisions. It also suggests that influence may operate without an individual being conscious of it."[30]

On the need for specific and concrete mechanisms to root out bias, Pew's guidance highlights that other research-based food regulators, such as those in Europe, require public disclosure of conflicts, and that requirements for conflicts should be stricter than those for FDA advisers given GRAS reviewers' critical role in determining whether the public is exposed to a use or ingredient.[31] Moreover, as FDA's draft guidance makes clear, proving an actual conflict of interest should not be necessary; instead, the presence of a potential conflict should be sufficient to raise questions about the integrity of the process and undermine public confidence in the safety of GRAS substances.

The case study of caffeine: The tailoring of scientific assumptions in GRAS determinations demonstrates the bias inherent in a secret, industry-dominated process.

As the 2013 JAMA Internal Medicine makes clear, the notion that regulated industries or their agents are well equipped to undertake an objective scientific study of the very products they are seeking to bring to market is naïve at best and dangerous to consumers at worst.[32] Other research documents significant effects related to bias on study outcomes.[33] Bias is apparent not

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[29] For example, Nancy Rachman, a regulatory scientist with experience conducting risk assessments for food additives and other chemicals, noted the following issues related to GRAS determinations:

> "In addition to managing the potential for expert bias due to COI… two other aspects of any regulatory process … are important for confidence in any decision: communication and transparency… and steps to ensure the consistency and integrity of the scientific basis for decisions. The less transparent a decision is, including its process and scientific basis, the greater the concern about the potential for COI [conflicts of interest] will be. GRAS has real transparency challenges…the food science, food toxicology and food regulatory community (including FDA) have not done an adequate job of explaining some important aspects of GRAS."

Comments from Nancy J. Rachmann, GRAS consultant, to Tom Neltner, on *Draft Guidance for Industry on Selection of Experts Conducting "Generally Recognized as Safe" (GRAS) Evaluations* 1-2 (Aug. 21, 2013).

[30] Comments from Lisa Lefferts, Senior Scientist, CSPI, to Tom Neltner, on *Draft Guidance for Industry on Selection of Experts Conducting "Generally Recognized as Safe" (GRAS) Evaluations* (Aug. 1, 2013).

[31] Pew Draft Guidance, *supra* note 25, at 6-7.

[32] JAMA Study, *supra* note 8.

[33] Research documents significant effects related to funding or other forms of bias in the outcomes of studies, and industry sources of funding for research have been found to have significant impacts on outcomes of studies. *See, e.g.*, A. Lundh et al., *Industry Sponsorship and Research Outcome*, The Cochrane Collaboration (2013) (finding in a review of 48 papers on drugs and medical devices, that "industry sponsored drug and device studies are more favorable to the sponsor's products than non-indussry sponsored drug and device studies due to biases that cannot be explained by standard risk of bias assessment tools."); Lenard Lesser, Cara Ebbeling, et al., *Relationship between Funding Source and*

only in outcomes, but in the myriad decisions that go into the categorizations and questions asked, and the multiple other informed judgments that shape study design.[34]

We examined GRAS determinations by companies for caffeine, and found evidence that bias affected those determinations. While we largely lack public view of the GRAS determinations made secretly by companies, secret GRAS determinations on caffeine that were solicited by FDA (and later obtained by the commenters through a Freedom of Information Act request) provide a rare glimpse into the wide variance in scientific parameters, assumptions and judgments that affect GRAS determinations. What one would expect to see in a system rife with bias is that the assumptions used as the basis for decisions vary, even for the same substance, and appear "tailored" to produce a particular outcome. That is precisely what we found when FDA conducted a limited review of the GRAS status of caffeine.

Although caffeine in cola-type beverages is limited by regulation to 72 milligrams per 12 ounces,[35] caffeine is a product that industry has self-determined to be GRAS for many other novel applications, even while it poses safety risks to consumers. In June 2013, FDA requested information from companies that had self-determined the GRAS status of caffeine in their products. The agency asked each company how it had determined that its products and their proposed uses met the standards for GRAS.

This is one of the rare instances in which the public has gained a view into the secret GRAS self-determination process, and the results are instructive. The companies' responses expose large inconsistencies and deficiencies in their determinations. For example, when considering worst-case scenarios for ingestion of caffeine, many of the companies assumed unrealistically low levels of exposure. Jelly Belly, for instance, noted exposure levels resulting from just two to three servings of its "Extreme Sports Beans" (caffeinated jelly beans),[36] even though the product is sold in units that contain 24 packaged servings and has an appearance that a consumer could easily confuse with non-caffeinated candy.

Conclusion among Nutrition-Related Scientific Articles, 4 PLoS Med 41-46 (2007) (finding that studies sponsored exclusively by food/drinks companies were four to eight times more likely to have conclusions favorable to the financial interests of the sponsoring company than those which were not sponsored by food or drinks companies); Anke Huss et al., *Source of Funding and Results of Studies of Health Effects of Mobile Phone Use: Systematic Review of Experimental Studies*, 115 Env. H. Persp. 1-4 (Jan. 2007) (finding that studies of the health effects of cellular telephone use that were "funded exclusively by industry … were least likely to report a statistically significant result."); Paul Ridker & Jose Torres, *Reported Outcomes in Major Cardiovascular Clinical Trials Funded by For-Profit and Not-for-Profit Organizations, 2000-2005*, 295 JAMA 2726 (May 17, 2006) (finding that recent cardiovascular trials funded by for-profit organizations are more likely to report positive findings than trials funded by non-for-profit organizations: while non-profits' studies favored new treatments in 49 percent of case, studies funded by for-profits favored new treatments in 67 percent of studies, and approximately the same results held when only randomized trials were considered).

[34] David Michaels, *It's Not the Answers That Are Biased, It's the Questions*, The Washington Post, July 15, 2008, http://www.washingtonpost.com/wp-dyn/content/article/2008/07/14/AR2008071402145.html.

[35] 21 C.F.R. § 182.1180.

[36] Letter from John Di Giusto, General Counsel, Jelly Belly Candy Company, to Michael Landa, Director, Center for Food Safety and Applied Nutrition (June 24, 2013) (on file with CSPI).

More troublingly, the companies did not adequately consider whether consumers have already ingested caffeine from other sources, as would be required for a meaningful assessment of the cumulative effect of the substance. A consumer could easily drink a coffee before consuming a large quantity of caffeinated jelly beans, for instance. None of the companies factored in caffeine exposure from other sources when considering worst-case exposure scenarios.[37] In fact, Jelly Belly specifically (and implausibly) stated that other sources of caffeine need not be considered because consumers would replace their other sources of caffeine with their Jelly Belly.

The responses that companies submitted to FDA regarding 90th percentile intake of caffeine reveal further discrepancies and inadequacies with regard to exposure estimates:

- Kraft assumed 90th percentile consumption levels ranging from 2.3 mg/kg/day to 5.2 mg/kg/day, which in a 70 kg person would amount to 161 to 364 mg of caffeine.[38]
- Pepsi assumed 90th percentile caffeine levels at 392 mg per day for adults over the age of 20.
- Coke cited a 90th percentile of 406.3 mg per day for adults over 18.[39]
- Monster assumed an even higher 90th percentile intake of 8.6 mg/kg, or 600 mg/day for a 70 kg person.[40]

In addition, Monster noted that per capita intake of caffeine is approximately 300 mg/day,[41] which is significantly higher than the lower range of 90th percentile consumption assumed by Kraft. Monster was also the only company that mentioned 90th percentile caffeine intake for adolescents, which it stated to be less than 225 mg/day.[42]

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[37] This ignores FDA's guidance for intake estimates of direct additives, which requires the petition process to consider "[a]ny anticipated increase in consumption from its petitioned use(s), if the food additive is also a naturally occurring material. The concentration of the additive occurring naturally in food(s) and an estimate of the level of consumption of the food(s) should be provided." U.S. Food and Drug Administration, *Guidance for Industry: Recommendations for Submission of Chemical and Technological Data for Direct Food Additive Petitions* (March 2009), available at http://www.fda.gov/Food/GuidanceRegulation/GuidanceDocumentsRegulatoryInformation/IngredientsAdditivesGRASPackaging/ucm124917.htm#intake.

[38] Letter from Kraft Foods Group, Inc., to Michael Landa, Director, Center for Food Safety and Applied Nutrition 9 (Aug. 5, 2013) (on file with CSPI).

[39] Letter from Rene Lammers, Chief Science Officer, PepsiCo, to Michael Landa, Director, Center for Food Safety and Applied Nutrition 2 (Aug. 1, 2013) (on file with CSPI); Letter from Rhona Applebaum, Vice President and Chief Science & Health Officer, The Coca Cola Company, to Michael Landa, Director, Center for Food Safety and Applied Nutrition (Aug. 1, 2013) (on file with CSPI).

[40] Letter from Miriam Guggenheim, Counsel to Monster Beverage Company, to Michael Landa, Director, Center for Food Safety and Applied Nutrition 6 (June 24, 2013) (on file with CSPI).

[41] *Id.*

[42] *Id.* at 7. Adolescents are a vulnerable population when it comes to caffeine. *See Scientific Report of the 2015 Dietary Guidelines for Americans Committee* 8-9 (Feb. 2015) ("The marketing and availability of high-caffeine beverages and products is on the rise. Unfortunately, only limited evidence is currently available to ascertain the safety of high caffeine intake (greater than 400 mg/day for adults and undetermined for children and adolescents) that may occur with rapid consumption of large-sized energy

Variability in the sources of data on which companies rely is also cause for concern. Jelly Belly, for instance, examined outdated caffeine consumption data from nearly 60 years ago.[43] Many of the companies relied on data from foreign markets, where consumption trends may differ from those in the United States. Monster cited a survey conducted by researchers at Penn State University[44] that found that 4 percent of Americans who consume caffeine consume energy drinks.[45] This rate is higher than rates found in studies cited by both Monster and Rockstar based on Canadian consumption. One such study mentioned by the companies found that only 1.5 percent of Quebecois teenagers consumed energy drinks daily,[46] while another found that only 1 percent did—while small in order, one of these estimates is fifty percent higher than the other, which would alter the estimate significantly.[47]

The submissions also fail to seriously consider important risks associated with the intended use of caffeine. For example, while the companies consider lethal doses in their GRAS determinations, the amount of caffeine known to produce non-permanent harm, such as anxiety, nausea, and sleeplessness—which are less severe but still significant—receives scant attention. The possibility of non-fatal side effects, for instance, is not even addressed in Jelly Belly's response. Kraft's response notes that consumption of an entire bottle of its MiO caffeine concentrate would result in exposure of approximately 1,000 mg of caffeine; according to Kraft's own assessment, this amount presents a reasonable likelihood of adverse effects in children.[48] But Kraft disregards this danger and instead assesses its product according to the more serious but less likely possibility that it might cause a severe adverse event, which Kraft defines as one "requiring medical intervention to manage, mitigate or prevent progression to a life-threatening situation."[49]

Red Bull and Rockstar similarly devote negligible attention to the risk of harm in their responses. Pepsi and Coke acknowledge the potential for caffeine to cause anxiety and sleep disturbance but dismiss these concerns, citing studies that show that caffeine use is self-limiting,

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drinks. Limited data suggest adverse health outcomes, such as caffeine toxicity and cardiovascular events.... Limited or no consumption of high caffeine drinks, or other products with high amounts of caffeine, is advised for children and adolescents.").

[43] Letter from John Di Giusto, *supra* note 36.

[44] D.C. Mitchell, et al., Supported by Washington (DC): International Life Sciences Institute, *Beverage Caffeine Intakes in the U.S.* (2013) [Poster presented at EB 2013 in Boston, ASN Meeting, April 22, program number: 848.12, abstract number: 7769].

[45] Letter from Miriam Guggenheim, *supra* note 40, at 7.

[46] Institut de la Statistique du Quebec, *Frequence de consommation habituelle de certaines boissons sucrees, eleves du secondaire*, Tableau A3.2, L'Enqu~te quebecoise sur la sante des jeunes du secondaire 2010-2011: TOME 1: Le visage des jeunes d'aujourd'hui: leur santti physique et leurs habitudes de vie (2012).

[47] Reseau du sport etudiant du Quebec, *Enquete Quebecoise sur le Marketing de la Malbouffe: 10 000 Jeunes se Prononcent!* (2011).

[48] Letter from Kraft Foods Group, *supra* note 38, at 8. (Noting that the probability of adverse side effects is considered "low-medium" for ingestion rates between 500 and 1,000 mg of caffeine and "medium" for rates between 1,000 and 1,500 mg). This contrasts with the DSM-5 which states that caffeine intoxication can occur "with low doses (e.g., 200 mg) in vulnerable individuals such as children, the elderly, or individuals who have not been exposed to caffeine previously.").

[49] *Id.*

although consumers would inevitably suffer adverse effects before deciding to limit their intake.[50] And Monster, though it mentions in passing the potential behavioral effects of caffeine on children, ultimately disregards them. This is an especially glaring omission considering that teenagers are the most frequent users of energy drinks and adverse effects are more likely to occur in consumers who are caffeine-naïve and have lower body weights.[51] As Monster notes in its response, a study of caffeine-naïve children found that ingestion of less than 50 mg of caffeine per day produced effects such as restless behavior and difficulty sleeping.[52]

The responses also specifically confirm the potential for conflicts of interest in GRAS determinations. Kraft, for instance, used an in-house toxicologist to conduct the company's determination. The toxicologist determined that 60 mg of caffeine per 8-ounce serving was GRAS, even though that is 25 percent higher than the amount determined by FDA to be GRAS when used in a cola beverage.[53] Monster also made its own GRAS determination, and later hired consultants to prepare a safety assessment "(t)o help ensure the independence of the GRAS determination."[54] The rest of the companies commissioned consulting firms and toxicologists.

The significant discrepancies in many of the most basic assumptions needed for a safety assessment indicate that some companies, in making GRAS safety determination, are likely to adjust core scientific assumptions to meet their own perceived needs, just as the literature on bias suggests.

III. The recommendations in FDA's draft Best Practices Guidance for Convening a GRAS Panel would improve the integrity of GRAS panels insofar as they are followed, although additional steps are needed.

While recognizing the current system's serious shortcomings, we hope that, someday, a reasonable system of oversight for GRAS is created, and that the bias and conflict of interest provisions will be an effective and legally mandated aspect of such a system. Although we find many reasons to be critical of the draft guidance and the severe limitations of the regulatory context in which it is being offered, there are specific aspects of the draft that are useful and that would improve the GRAS decision-making process if followed by industry.

Conversely, nothing in our comments below should be misunderstood to undercut our fundamental position that GRAS determinations—and the bias and conflicts of interest related to them—should be reviewed by FDA and be made publicly available. As Pew's draft conflict of interest guidance similarly notes in its introduction, nothing in the comments below "should be construed" as endorsement of the "view that the food industry is authorized by the" FAA to

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[50] Letter from Rene Lammers, *supra* note 39, at 18; Letter from Rhona Applebaum, *supra* note 39.
[51] F. Castellanos & F. Rapoport, *Effects of caffeine on development and behavior in infancy and childhood: a review of the published literature*, 40 Food & Chemical Toxicology 1235-1242 (2002).
[52] *Id.*
[53] 21 C.F.R. § 182.1180 (caffeine up to a level of 0.02 percent (200 ppm) is generally recognized as safe (GRAS) for use in cola-type beverages).
[54] Letter from Miriam Guggenheim, *supra* note 40, at 1.

"make its own final GRAS determinations without FDA review."[55] Similarly, we also maintain that FDA's guidance "be used irrespective of whether the law is so construed."[56]

With such caveats, we support many of the specific provisions in the agency's proposal and explain the reasons for our support below. Specifically, we agree that to determine that there is a general recognition of safety among knowledgeable experts, at a minimum, the statements below should be true:

1) GRAS panel members must have appropriate and balanced expertise;
2) Bias, as well as the appearance of bias, should be addressed with concrete steps to address and counter it; and
3) Data and information provided to a GRAS panel should be limited to publicly available information and should exclude trade secret or other forms of proprietary information.

In addition, we would highlight that the aspects of the Best Practices in Convening a GRAS Panel Guidance that emphasize written and public disclosure of conflicts and of the basis for GRAS determinations are essential. Below, we address the sections of the draft guidance in the order in which they appear in FDA's proposal.

FDA Should Address the Potential for Bias and Adopt Policies Relevant to the Context of a GRAS Panel

FDA's draft guidance (Section III) includes a range of observations on bias and reviews a number of relevant potential models. It notes that at that outset that a balance of appropriate expertise that reflects the matter under consideration is essential to a sound decision. We agree with both the FDA and the National Academies of Sciences, Engineering and Medicine (NASEM) that the "failure to include an appropriate discipline can compromise the quality of a panel's analysis and judgments, and that, even within a particular discipline, there may be important differences and distinctions within the field that require careful consideration in the committee composition and appointment process."[57]

FDA describes NASEM's policies on the subject of balance as "emphasizing that the knowledge, expertise, and perspectives of potential members of a committee convened by the NASEM must be thoughtfully and carefully assessed and balance in terms of the subtleties and complexities of the particular scientific, technical and other issues to be addressed" as well as the "functions of the committee."[58]

We concur with the draft guidance that a range of procedural considerations can also bias a committee or panel's deliberations. FDA, citing a report from the National Academy of Medicine (NAM), highlights considerations such as: real or perceived status differences among

[55] Pew Draft Guidance, *supra* note 25, at 1.
[56] *Id.*
[57] Draft Guidance, *supra* note 13, at 9.
[58] *Id.*

group members; leadership of the effort; and the omission of information or the specific ways that information is presented.[59]

As the draft guidance describes, to ascertain the extent of a conflict of interest, the core question that FDA asks with regard to other processes is whether the issue is "a particular matter" with a "direct and predictable effect" on the financial interests of any organization. We agree, as the instant draft guidance observes, that decisions by a GRAS panel are a "particular matter" that should trigger a thorough examination of the potential for actual and perceived conflicts of interest among panel members.

Similar to the draft guidance, we would highlight the distinction between the FDA's use of *advisory* committees, which provide recommendations on matters for which FDA is the ultimate decision maker, and GRAS determinations, in which FDA is not the decision maker. (For secret GRAS determinations, FDA has no input at all; for GRAS notifications, FDA has, due to its own final rule on GRAS, unduly circumscribed its authority).[60] Given the importance of decisions made by GRAS panels as well as the financial stakes, one implication is that the protections against conflicts of interest in the GRAS context (which, by definition, concern a particular matter that raises the prospects of a conflict) would need to be far greater than those applied to advisory committees.

The guidance further observes that the factors provided by other current FDA guidance in assessing whether to obtain a waiver for advisory committee members shows the limitations of current practice, and points out that it should be augmented by a public process through which GRAS panelists must disclose conflicts:

> While the advisory committee process has some similarities to the GRAS panel process, there are some important differences between FDA's advisory committee process and the GRAS panel process. One difference is that the statutes and regulations applicable to FDA's advisory committee process expressly provide for circumstances in which FDA may grant a waiver that would allow an individual to participate in an advisory committee meeting, in either a voting or non-voting capacity, even though the individual has a conflict of interest (Ref. 19 and Ref. 21). FDA discloses such waivers as part of the record of the advisory committee process (Ref. 21). In contrast, if a proponent allows an individual to participate in a GRAS panel, in either a voting or non-voting capacity, even though the individual has a conflict of interest, there generally would not be a public process (such as a public meeting) whereby the proponent could disclose the conflict and the reasons for waiver; the lack of a public process to make a "waived" conflict of interest transparent presents a challenge to the proponent of the substance for waiving a conflict of interest or an appearance issue without undermining the credibility of the GRAS panel's opinion.[61]

We agree, and note that this credibility is particularly strained where, as with GRAS, the agency retains no decision-making role.

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[59] *Id.* at 10.
[60] *Id.* at 11.
[61] *Id.* at 13.

Underscoring this point, FDA also notes that, for NASEM, prompt and public disclosure of a conflict is required for an individual to serve on a committee where a conflict of interest could "significantly impair the [] objectivity" of the member or "create an unfair competitive advantage for any person or organization." GRAS panels are specifically at risk for both forms of conflicts. In addition to the issue of an individual's objectivity discussed above, the NASEM guidelines are illuminating in that they provide an additional lens with which to examine the context applicable to a GRAS determination, which is an assertion of a competitive advantage. Potentially, this category of conflict of interest, if unchecked, generates a "race to the bottom" in which panels disregard their scientific and legal obligations to secure competitive advantage for their clients.

As cited in the draft guidance, a special committee of the National Academy of Medicine (NAM) separately has defined conflicts of interest as a "set of circumstances that creates a risk" of a conflict. The NAM's report further outlines additional factors that can constitute conflicts of interest, including financial interests, which "does not have to be great for the influence to be undue," as well as secondary interests like "professional advancement, personal achievement, and favors to friends, family, and colleagues."[62] Such conflicts are also recognized by the National Comprehensive Cancer Network (NCCN), which address "organizational affiliations, activities or other interests that impair objectivity or create an unfair competitive advantage."[63] We note that GRAS determinations, which are being made by a closed panel of professional colleagues who are all being compensated by the same company, are in particular jeopardy of succumbing to such bias. Furthermore, as noted above, some experts are repeatedly hired to serve on GRAS panels, increasing the risk of a conflict.

As to the remedy, the NAM views disclosure as "necessary but insufficient" and recommends that "disclosures be sufficiently specific and comprehensive (with no minimum dollar threshold) to allow others to assess the severity of the conflict."[64] The NAM further recommends that a chair without a conflict be appointed, and that disclosures of conflicts be public. The NCCN calls for public disclosure, exclusion of conflicted members, recusal of members, and removal from eligibility to serve following a high number of recusals.

We agree that prompt and public disclosure of conflicts is both necessary and insufficient and suggest that these analyses show that FDA would need additional tools—including recusal and removal—to alter the "set of circumstances" that currently applies to GRAS determinations —circumstances that create the possibility of professional and competitive conflicts of interest.

The FDA's draft guidance also references other protocols, including that of the Flavor and Extract Manufacturers Association (FEMA) and notes that FEMA retains a conflict of interest policy.[65] Contrary to FDA's emphasis on publicly available data in the draft guidance, it appears that FEMA's GRAS determinations are sometimes based entirely on unpublished safety data.

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[62] *Id.* at 14.
[63] *Id.* at 15.
[64] *Id.*
[65] FEMA Expert Panel Conflict of Interest Protections and Procedures (*available online at* https://www.femaflavor.org/gras#conflict).

For example, in 2013, FEMA issued GRAS determinations for four new flavorings.[66] When nonprofit groups sought data on these new substances, the organizations found *no* relevant published safety data, toxicology data, or exposure data.[67] When the groups asked FEMA for published data on the four substances, it responded that there was none.[68] Similarly, when CSPI submitted to the FDA a Freedom of Information request for all correspondence and documentation relating to several sweetness-enhancing substances that had been determined to be GRAS by FEMA, FDA sent a letter stating that it found "no responsive information."[69] After more than a year of meetings and correspondence, CSPI finally succeeded in obtaining from FEMA unpublished studies on the sweetness enhancers.[70] As FDA's draft guidance implies, a practice of relying on unpublished data cannot satisfy the legal requirement that there be a "general recognition" of safety for a condition of use.

All of the factors that can create conflicts of interest for panels—including financial interests, competitive advantage and professional identification and status—apply in spades to the FEMA operation, and none of the remedies, including public disclosure, appears to be in place. A 2015 *Time Magazine* article, *Meet the Secret Group that Decides Which Flavors Are 'Natural'*, describes FEMA as "a secretive food industry trade group that has no in-house employees, no office of its own and a minuscule budget" that "serves as the de-facto regulator of the nation's flavor additives:"

> The Flavor and Extract Manufacturers' Association companies—which produce 95 percent of all flavors on the market in the United States—typically forgo FDA review and instead choose to submit their flavors to the trade association for a safety review. A standing panel of six to eight scientific experts oversees the trade group's safety program and determines whether ingredients are generally understood to be safe by the scientific

[66] These were: FEMA GRAS No. 87: *trans*-6-Octenal (also known as (*E*)-6-Octenal or (*E*)-Oct-6-enal); FEMA GRAS No. 4798: 2-(((3-(2,3-Dimethoxyphenyl)-1*H* -1,2,4-triazol-5-yl)thio)methyl)pyridine (also known as 2-((5-(2,3-Dimethoxyphenyl)-2*H* -1,2,4-triazol-3-ylthio)methyl)pyridine or Pyridine, 2-(((3-(2,3-dimethoxyphenyl)-1*H* -1,2,4-triazol-5-yl)thio)methyl)); FEMA GRAS No. 4802: (S)-1-(3-(((4-amino-2,2-dioxido-1*H*benzo[c][1,2,6]thiadiazin-5-yl)oxy)methyl) (also known as piperidin-1-yl)-3-methylbutan-1-one); FEMA GRAS No. 4809: 2-(4-Methylphenoxy)-*N* -(1*H* -pyrazol-3-yl)-*N* -(thiophen-2-ylmethyl)acetamide (also known as *N* -(1*H* -pyrazol-5-yl)-*N*-(thiophen-2-ylmethyl)-2-(ptolyloxy)acetamide)

[67] Letter from NRDC, CSPI, CFS, Center for Environmental Health, and Environmental Working Group to Michael Taylor Re: Flavors and FEMA GRAS Program (Sept. 18, 2014) (on file with CSPI).

[68] *Id*. It did, however, offer to make 7,000 pages of unpublished data available to NRDC for a processing fee of more than $1,000.

[69] Letter from Sharon R. Dodson, FOI Technician, Office of Food Additive Safety, Center for Food Safety and Applied Nutrition to Alison Brown, Center for Science in the Public Interest Re: FOI Request No. 2012-485 (Feb. 21, 2012 but sent via email on August 10, 2012).

[70] As documented in letter from Michael F. Jacobson and Lisa Y. Lefferts, Center for Science in the Public Interest to Dennis Keefe, Director, Office of Food Additive Safety, Center for Food Safety and Applied Nutrition (January 31, 2013).

community. These experts, who are paid by the trade association, review published and unpublished data before making a conclusion on the safety of an ingredient's use.[71]

We note that the stringency of the FEMA review process appears to have relaxed significantly in the wake of FDA's 1997 GRAS rulemaking proposal. Originally, FEMA contracted with FDA to publish safety data underlying GRAS determinations for flavorings. These reviews were published on a periodic basis during the 1970s and formed the basis for the GRAS affirmation (GRASa) Program, which operated from 1975 to 1985. Following the end of the GRASa Program, there was a steep decline in GRAS determinations for flavorings; however, in the wake of the 1997 proposal, "there has been a significant increase in the number of substances GRASed [*i.e.*, with completed GRAS determinations] annually" by FEMA.[72]

In addition, FEMA's review process is a standing panel, contrary to the recommendations in the draft guidance that *ad hoc* panels designed to contain expertise appropriate to the considerations of the particular matter are preferred. Given the lack of independence in FEMA's process, we agree that the draft Guidance is correct that *ad hoc* panels may be more appropriate as a limited corrective. (A truly independent standing panel, with features shared by advisory committees, such as term limits and bars on *ex parte* communications, does remain a good model but is not at all what FEMA's structure provides.) The draft's cursory and uncritical treatment of the FEMA process, with its profound conflicts and lack of public oversight, is very concerning.

Specific Comments on the Recommendations in the Draft Guidance

We strongly support the overall recommendations that FDA provides, although we believe that these are necessary but insufficient to resolve the problems with the credibility of the process as it now exists. Specifically, we support FDA's recommendations that, at a bare minimum, it is necessary to:

- Assess and balance the knowledge, experience, and perspectives of potential GRAS panel members in terms of the subtleties and complexities of the particular scientific and technical issues applicable to the food substance and its intended use in human food or animal food;
- Consider and take steps to address procedural issues associated with the organization and deliberations of the GRAS panel;
- Consider and take steps to assess potential GRAS panel members for conflicts of interest and appearance issues;
- Document how the proponent or organizer applied the written GRAS panel policy to the selection and vetting of each member of the GRAS panel; and
- Take steps to provide transparency and clarity regarding the selection and vetting of each member of the GRAS panel.

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[71] Erin Quinn and Chris Young, *Meet the Secret Group that Decides Which Flavors Are 'Natural,'* Time, June 9, 2015 (*available online at:* http://time.com/3913232/natural-flavoring-government/).
[72] R.L. Smith et al., *GRAS Flavoring Substances 24*, Food Technology 46-48 (June 2009).

However, both a proponent and the proponent's organizer face conflicts of interest that prevent them from independently and credibly carrying out these essential tasks without bias.

The FDA implies in the guidance that a GRAS safety determination based on *scientific procedures*, as opposed to *use before 1958*, should be made by an expert panel consistent with the guidance. The guidance itself identifies no circumstances under which a panel would be unnecessary to make a determination based on scientific procedures. The FDA's draft Guidance should clarify, based on the agency's GRAS final rule, when a GRAS panel is required to make a GRAS safety determination.

Specifically, in lieu of a GRAS panel's determination of safety, FDA's final rule on GRAS requires a mechanism to demonstrate that a substance is safe under the conditions of use. According to FDA, these mechanisms include:

- publication in the primary, peer-reviewed scientific literature; publication in the secondary scientific literature;
- documentation of the opinion of an ''expert panel'' that is specifically convened for this purpose;
- the opinion or recommendation of an authoritative body such as the National Academy of Sciences or the Committee on Nutrition of the American Academy of Pediatrics on a broad or specific issue that is related to a conclusion of GRAS status; and
- technical literature from JECFA [the Joint FAO/WHO Expert Committee on Food Additives] can provide evidence that generally available safety data and information are generally accepted.[73]

If the final guidance does clarify this point, we note that we agree with FDA's prior conclusion that JECFA should not be listed as an authoritative body for the purpose of this guidance, since JECFA uses both published and unpublished data.[74] We also disagree that technical literature from JECFA can be used to provide evidence that generally available safety data and information are generally accepted, due to JECFA's practice of using unpublished data. These conclusions are aligned with the draft guidance because members and FAO

[73] *See* Substances Generally Recognized as Safe, *supra* note 11, at 54975. FDA also "stated that there could be a basis to conclude that there is expert consensus that the published results of a particular safety study (*i.e.*, the primary scientific literature) establish the safety of a substance for its intended use if the study raises no safety questions that experts would need to interpret and resolve." *Id.*

[74] FAO Joint Secretariat to JECFA, Joint FAO/WHO Expert Committee on Food Additives, FAO procedural guidelines for the Joint FAO/WHO Expert Committee on Food Additives. Rome, Feb. 2003, (available online at: http://www.fao.org/fileadmin/templates/agns/pdf/jecfa/2003-02-24_Food_Add_Cont_Guidelines.pdf). The guidelines state that "[m]anufacturers have the responsibility to provide all relevant published and unpublished data that are available on the food additives on the agenda, as described in the *Call for data* issued by the Joint Secretariat. Confidential information pertaining to manufacturing trade secrets (such as manufacturing processes), is submitted, should be clearly identified so that this information will not be published."

consultants with actual or potential conflicts of interest are not precluded from participating in evaluations.[75]

FDA further states that "[w]hether the findings of a GRAS panel, a determination by an authoritative body, or a peer-reviewed scientific study provide sufficient evidence that safety data and information are generally accepted would depend on the specific findings of the GRAS panel, the specific determination by the authoritative body, and the data and information in the peer-reviewed scientific study rather than on the classification of the mechanism for providing evidence that safety data and information are generally accepted."[76] Although they are far from a model of clarity, such assertions belong, for context, in the final version of this guidance as well.

There are three additional practices typically used by FDA and other agencies for advisory committees that should also be used for GRAS panels:

Inclusion on GRAS panels of technically qualified, bona fide consumer representatives who are also technically qualified.

Similar to consumer representatives on FDA advisory committees, the representative would need to be scientifically qualified and have affiliations with and/or actively participate in consumer organizations. The inclusion of *bona fide* consumer representatives who are technically qualified would provide a better balance of viewpoints on the panel, would ensure that panels are a more representative proxy for the larger scientific community, and would substantially improve their transparency.

Limits on the participation of specific individuals on GRAS panels.

Currently, advisory committee members serve for a term (up to four years), and within that term their service is in practice further limited (*e.g.*, to a few meetings, generally ranging from none to four a year). In any case, as Special Government Employees, advisory committee members may not serve more than 130 days during any period of 365 consecutive days (due to hiring limitations, but with ancillary effects on conflicts).

In contrast, as noted previously, some individuals repeatedly serve on multiple GRAS panels, year after year. The JAMA Study noted that at least 10 individuals served on 27 or more panels, while one person served on 128 of the total 290 panels.[77] This practice greatly increases the probability of a "set of circumstances that creates a risk" of a conflict.[78] It can provide a

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[75] *Id.* They are required to disclose in writing all circumstances that could lead to potential conflicts of interest. The Committee discusses and adopts a decision whether the scientist may participate in the evaluation or not: "Both Members and FAO Consultants are required to disclose in writing all circumstances that could lead to potential conflicts of interest. When an interest is declared on a particular substance, the Committee will discuss and adopt a decision whether the scientist may participate in the evaluation of this substance."

[76] Substances Generally Recognized as Safe, *supra* note 11, at 54975.

[77] JAMA Study, *supra* note 8, at E4.

[78] Draft Guidance, *supra* note 25, at 14.

financial incentive to make determinations favorable to proponents so that these individuals can continue to depend on a steady stream of money from serving on GRAS panels. Individuals serving on GRAS panels should be limited to serving on, for example, no more than one or two panels per year. Continual changes of personnel would help to keep the process vigorous and make it less likely that groups will customarily "rubber stamp" determinations.

Guidance and limits on compensation.

Advisory committee members are generally retained, designated, appointed, or employed to perform temporary duties, and that is the nature of the program. This is also the situation with GRAS panel members. While those serving on advisory committees do receive a salary for each meeting day as well as travel and per diem costs, they are not compensated for their time preparing for meetings and compensation rates are fixed. Similarly, general limits on compensation should be recommended for GRAS panel members.

With the above caveats, our additional specific views on the steps recommended by FDA are below and are headed with the ordering system used in the draft guidance.

B.1. FDA Should Not Permit Employees, Attorneys or Agents of the Proponent to Participate at All

The FDA indicates that an individual with specialized expertise who is employed in some fashion by the proponent could participate as a "non-voting" member or advisor to panels if that person's expertise "could be helpful."[79] Given the discussion of the sources of bias, above, which encompass professional status, financial incentives, and the leadership of a group, and the lack of commensurate safeguards including disclosure, we strongly disagree that it would be appropriate for employees of any company with a financial interest in the particular matter at issue to participate in any way in the evaluation of the safety of a substance based on general recognition.

The employee, whether acting as an advisor or non-voting member, could signal to the group, through his or her presentation of the data and conclusions, what a company's interests and views are, and the employee's participation would, by itself, add pressure to the process and utterly undermine the credibility of the panel's decision. This financial relationship presents a conflict of interest because scientists may feel pressure to reach favorable conclusions for the companies that employ them.[80]

Should the panel have a question that is not resolvable based on the expertise of the panel members or that requires additional scientific insight, it should first evaluate whether the panel's composition, including its experts, requires adjustment or addition. Second, it should assess whether it would be appropriate for the panel to ask an appropriate and objective expert to provide an answer to the panel and then to leave the panel's deliberations. The company itself should be involved only to the extent that it uniquely can provide relevant factual information (*e.g.*, on proposed uses), but this should be conveyed in writing.

[79] *Id.*, at 19.
[80] *See, e.g.*, research *supra* note 33.

Taking such steps would be important in light of the concerns highlighted by the NASEM guidelines regarding assertion of a competitive advantage. Without such safeguards, we are concerned that there could be a "race to the bottom" in which panels are pressured to disregard their scientific and legal obligations to secure competitive advantage for their clients.

B.2. Additional Appropriate Expertise

We concur with the general principle that a GRAS panel's composition should be considered to create "expertise that reflects the physical, chemical, and biological properties of the food substance and the scientific questions that arise in relation to the conditions of its intended use." It is critical, first and foremost, that every panel include members with expertise in chemistry or biochemistry, as well as toxicology and exposure assessment. In addition, one individual should not occupy more than one of those roles, and their core expertise should be supplemented as FDA recommends.

Table 1 in the draft Guidance lists examples of recommended expertise on a GRAS panel based on the conditions of intended use of a substance. These examples are useful but should be expanded. For example, expertise in pediatric or developmental toxicology is also needed for substances intended for use in infant formula, and expertise in gastroenterology is needed for microbial ingredients. For substances with a specific physiological effect, the guidance should explicitly mention that fetuses, infants, and children are relevant subpopulations.

We concur with the draft Guidance that, for changes in use, "the emphasis in selecting members of a GRAS panel should be on the expertise necessary to assess the change."[81] We are concerned that increased use levels of some substances, including such mainstream substances as caffeine and sugar, are likely to be inadequately evaluated for safety, and we would like to see language that recommends that reviews for increases in use take into account relevant scientific developments and include, as the safety standard requires, specific review of cumulative effects of a substance.

We further agree with the Guidance that "[i]f the intended use of the substance would be significantly different from existing uses, an individual with expertise in exposure assessment should evaluate the new estimated dietary exposure and one or more individuals with expertise in the potential toxicological or physiological effects of the substance under the new conditions of use should evaluate whether the available data and information support the safety of the substance under the new conditions of use."[82]

B.3. *Number of Members of a GRAS panel*

The FDA should provide more specific guidance on the number of GRAS panel members, rather than leaving it up to an inherently conflicted proponent to determine.[83] It appears implausible to us that three or fewer people could serve as a legitimate and balanced

[81] Draft Guidance, *supra* note 25, at 20.
[82] *Id.*
[83] *Id.*

proxy for the larger scientific community. As described above, several guidelines on bias also observe that panels with members evincing some bias should be balanced with more objective members and an objective chair for the process. As FDA notes, even if panels "contain a single expert of each applicable scientific discipline," this can mean that the panel lacks a "means for the GRAS panel as a whole to resolve questions" raised by that member.

We note that it is also wholly impractical and unreasonable for proponents to ascertain, *a priori* at the start of organizing the panel's process, whether the data being presented and the particular questions "raise no safety questions that experts would need to interpret or resolve," as FDA suggests, since ascertaining the answer to that question is the purpose of the panel's process.[84]

C. Procedural Issues with the Organization and Deliberations of a GRAS panel

We agree that a written GRAS panel policy "to address the potential for bias" should:

- Establish clear roles and responsibilities for each member of the GRAS panel;
- Establish clear decision-making procedures that the GRAS panel will follow; and
- Consider factors such as seniority or perceived status among panel members and the leadership skills of an individual who would be the formal leader of the GRAS panel (or likely to become the informal leader if the proponent or organizer does not appoint a formal leader).

We recommend that, rather than "specifying whether" the charge to the GRAS panel will "inform the members of the GRAS panel about the potential for bias," that FDA instead require that a charge to GRAS panels so inform the panel. For similar reasons, we agree with FDA that the "proponent [should] take appropriate steps to avoid influencing the deliberations of the GRAS panel—*e.g.*, by formulating the charge to the panel in neutral, unbiased language; limiting communication with the GRAS panel to the minimum necessary to manage the affairs of the GRAS panel efficiently and effectively; and then awaiting the outcome." As above, we also think that membership should include consumer representatives.

D. Assessment and Management of Conflict of Interest and Appearance Issues

We strongly agree that the written GRAS panel process for each determination should be publicly available and provide for transparency by allowing outside parties (which include members of the public) to assess the process used to assess and manage conflicts and appearance issues in members of the GRAS panel. We also concur that the written GRAS panel policy should include a process for identifying competing interests, including bias and appearance issues, and should specify how those are defined and addressed. We further urge FDA to adopt a broad definition of "affected entity," as the specific proponent may not be the sole source of actual or potential bias for an expert with deep industry (or industry trade association) connections or ties.

[84] *Id.*

We differ with FDA's categorizations of conflicts of interest and appearance issues and request changes in this Section as follows:

- Any compensation for services, including honoraria for service on the GRAS panel, can also be a source of COI and/or an appearance issue and so should not be excluded from Table 2 or redefined as mere "honoraria." A blanket exemption for "honoraria" could conceal payments in any amount. As we request elsewhere in these comments regarding limits on compensation, FDA's guidance should define the terms and limitations of honoraria, including that an honorarium policy be established and disclosed in advance as part of the written and publicly available GRAS panel policy. That written policy should, in turn, explicitly state that any honorarium/compensation is not expected to bind the recipient to provide a particular viewpoint, recommendation, or finding, clarify the amount of the honorarium, and provide that such compensation/honoraria will be given fairly to all panel members.
- To Table 2's last line, we would add: "other close family member," since such financial ties are a direct conflict, not merely an appearance issue.
- We would move up to Table 2 from Table 3 the line regarding "[h]aving or seeking a business, contractual, or other financial relationship with an affected entity." As the 2013 study found, many GRAS consultants maintain close business ties in an ongoing manner with proponents, and these would certainly constitute a conflict of interest, not merely an appearances concern.
- Similarly, being "an active participant in an organization that is an affected entity" is a clear conflict of interest, not merely a matter of appearances.
- We also would move the line regarding "[h]aving one's own work as a key element" of the science from Table 3 to Table 2, since that would represent a classic intellectual conflict and may impinge upon an expert's ability to be objective regarding the limitations of his or her own work.
- Last, we do not agree, per Table 3, that consistently and strongly advocating specific views or positions on a scientific issue relevant to safety assessment is *necessarily* an appearance issue. We would recommend that FDA instead note that the possibility for an appearance of conflict of interest may arise where a pattern or history of past decisions suggests disregard for objective application of the factors underlying a safety determination.

As to item 3, we agree that a written GRAS panel policy should, at the outset, establish "criteria for evaluating the significance of conflicts of interest and appearance issues." Such documentation, per item 4, must be made public, and should "promote clarity and transparency."[85] Moreover, it should, as FDA specifies, "document that the process used for identifying and managing" conflicts and bias was "implemented," including the specifics of decisions and factors for panelist members.

[85] *Id.* at 24-25.

We also generally concur with the factors identified in the guidance, though we urge FDA to set out in its final guidance some concrete parameters by which proponents should definitively rule out conflicted or biased experts from serving on a GRAS panel.

We also support the strategies that FDA identifies for managing conflicts, *except* that conflicted members should not merely be allowed as "non-voting members" or because the need for their expertise "outweighs the potential" for a conflict, as FDA suggests. Rather, for reasons more fully explained above, they should not be members at all. The FDA's discussion of waivers, Section 4, is unilluminating—rather than clearly specifying circumstances for a waiver, FDA appears to allow proponents to make the call, thus embedding further opportunities for a conflicted process.

While it may be true that the food industry has been allowed to work repeatedly with a finite number of experts, we strongly disagree that the field of potential GRAS panelists is as limited as FDA suggests in Section 3. We would urge the agency not to relax substantive standards for panels in the service of such industry complaints, particularly in light of the severe deficits of the program generally, as discussed above.

The FDA suggests that proponents use written GRAS policies and strategies to mitigate conflicts that should disqualify conflicted experts from serving on GRAS panels. This language should be struck, as it absolutely undermines the stated purpose of its guidance, creating significant (and unnecessary) tensions with the literature, standards, and best practices on bias avoidance that ground its recommendations. We would urge that FDA, in its final guidance, instead insist that consistently high standards for recruitment of GRAS panels be applied.

E. Information Provided to a GRAS panel

We agree with FDA that, to make a determination that a substance is "generally recognized as safe," qualified experts must be able to conclude that the substance is not harmful *without* access to, or reliance on, unpublished information, data, and methods. There can be no "general recognition" without a publicly cognizable basis for such a recognition.

Further, we agree that "there could be no basis for a conclusion of GRAS status if trade secret information (or other non-public information) is necessary for qualified experts to reach a conclusion that the notified substance is safe under the conditions of its intended use (81 FR 54960 at 55000)," as well as with FDA's recommendation that a "proponent or organizer minimize the amount of non-public information provided to a GRAS panel." We would suggest that presentation of trade secret or non-public information to assert that a substance is safe may bias a panel prior to a decision and raise the specter that a decision is based upon such information, and we would urge that FDA preclude the use of such information.

We also agree with FDA that non-public information that raises the possibility of safety concerns may be presented, but insofar as a decision regarding safety would necessarily reference these data and information, the GRAS panel's determination should publicly and fully outline such concerns as well as the data upon which the concerns are based. Again, a determination that a substance is safe based on general recognition by knowledgeable experts

necessitates that there be such general recognition based upon the full facts that should be available to such experts. As FDA indicates, doing so "is appropriate to make the data and information provided to the GRAS panel complete, representative, and balanced and would be consistent with the requirements we have established for a GRAS notice."[86]

We appreciate FDA's stated position in the draft that mere publication, by itself, of the opinion of a GRAS panel does not automatically obviate the need to make a GRAS determination. We urge FDA to further clarify that publication of the opinion of a GRAS panel based on non-public information would not satisfy the GRAS safety standard unless the non-public information is made public or is demonstrably inconsequential to the panel's determination.

F. Documenting the Deliberations and Conclusions of a GRAS panel

We agree that documentation of a panel's deliberations and conclusions should include the three elements identified by FDA,[87] in addition to the written materials on bias and conflicts discussed above.

We concur that each panel member should explicitly identify the data or information that "form the basis for his or her opinion," and also concur with FDA that panel members should avoid filling a gap in the data or information by applying merely theoretical considerations or prior experience. To be clear, GRAS panel members should rely on publicly available data to provide the basis for safety assessment, as we assert they must under the GRAS statutory standard.

Moreover, as FDA notes, because a GRAS panel is a "proxy" for the larger scientific community, panel members should demonstrate, as FDA recommends, how and why their views are representative of the views held broadly by scientists in their respective disciplines.

G and H. Considerations When a GRAS Notice is Submitted, or Not Submitted, to FDA

We disagree with FDA's assertion that in some cases, a proponent may choose not to make the opinion of a GRAS panel public. This assertion is utterly unsupportable in light of the strong emphasis on public disclosure contained in every model for the guidance reviewed and described by FDA. We think that in all cases, the proponent should make it public, as only public disclosure of the determination can fulfill the purposes of this Guidance in minimizing bias. Only public disclosure of determinations could possibly begin to address the profound conflicts that we have described and that are inherent in current GRAS safety determinations.

We agree with FDA that unfavorable information as well as favorable information (*i.e.*, whether it is consistent or not with a conclusion of GRAS status) should be submitted to FDA,

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[86] *Id.* at 25-26.

[87] FDA's three elements are: (1) The available data and information that the GRAS panel reviewed; (2) how the GRAS panel handled its deliberations; and (3) the basis for the conclusion of the GRAS panel. *Id.* at 26.

regardless of whether such information is publicly available. It should also be made publicly available regardless of whether it is submitted.

Whether submitted to FDA or not, any GRAS determination should not be based upon trade secret or other proprietary or non-public information, since these cannot be grounds for a "general recognition" of safety. We therefore do not understand why FDA would continue to allow proponents to proffer an explanation regarding "how there could be a basis for a conclusion of GRAS status if qualified experts (other than those on the GRAS panel) do not have access to such data and information."[88] We wonder what explanation could legally suffice and would urge FDA to clarify how it would evaluate the reasons provided.

Finally, we appreciate that FDA makes clear "any company that intends to market a food substance on the basis of an independent conclusion of GRAS status [should] carefully consider the recommendations in this draft guidance and to apply them to its own assembly and management of a GRAS panel." We are grateful that, even in such a limited fashion, FDA is emphasizing the obligation of industry to conduct a thorough safety evaluation.

Fundamentally, as FDA's assertions make painfully evident, this guidance remains an inadequate step to assure public safety given FDA's lack of oversight of GRAS more generally. We urge FDA to reconsider whether the structure of GRAS in fact permits the agency to adequately patrol the boundaries between GRAS substances and food additives, and whether its efforts to mitigate bias and conflicts of interest could ever be truly adequate unless full review and public disclosure of GRAS safety determinations is required.

[88] *Id.* at 27.