UNITED STATES DISTRICT COURT
SOUTHERN DISTRICT OF NEW YORK

CENTER FOR FOOD SAFETY and ENVIRONMENTAL DEFENSE FUND, *Plaintiffs*, *v.* ALEX M. AZAR II, SECRETARY, DEPARTMENT OF HEALTH AND HUMAN SERVICES, NORMAN E. SHARPLESS, ACTING COMMISSIONER, UNITED STATES FOOD AND DRUG ADMINISTRATION, and UNITED STATES FOOD AND DRUG ADMINISTRATION, *Defendants*.	)	No. 1:17-cv-3833 (VSB) (BCM)

OPPOSITION TO DEFENDANTS' CROSS-MOTION FOR SUMMARY JUDGMENT AND REPLY TO DEFENDANTS' OPPOSITION TO PLAINTIFFS' MOTION FOR SUMMARY JUDGMENT

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INTRODUCTION

Defendant Food and Drug Administration ("FDA") asks this Court to find that Substances Generally Recognized as Safe, 81 Fed. Reg. 54,960 (Aug. 17, 2016) (codified at 21 C.F.R. pts. 20, 25, 170, 184, 186 & 570) ("GRAS Rule"), is somehow consistent with its duties under the Federal Food, Drug and Cosmetic Act ("FFDCA" or "Act"), the Administrative Procedure Act ("APA"), and fundamental constitutional principles. To rule for FDA, the Court would have to find that the Agency is permitted to shift responsibility for key aspects of food safety to food manufacturers without retaining oversight, **and** allowing manufacturers to secretly self-certify substances as GRAS is consistent with FDA's food safety duties, **and** FDA's vague and lenient criteria for determining GRAS status are legally adequate. None of these findings is supportable.

FDA's defense of the GRAS Rule rests on three untenable contentions: FDA's ability to enforce violations of the FFDCA makes up for the fact that the GRAS Rule allows manufacturers to make GRAS determinations in secret with no agency oversight; the supposed impracticability of identifying *all* substances added to food justifies FDA's decision not to require notice when manufacturers certify substances to be GRAS; and FDA's decision to outsource food safety decisions to manufacturers is acceptable because it is efficient. These contentions ignore both the requirements of the FFDCA and record evidence documenting the dangers presented by the approach codified in the GRAS Rule.

FDA fails to acknowledge the hazards inherent in a regime that allows self-interested manufacturers to make decisions that could threaten public health and safety. But allowing the fox to guard the henhouse can have disastrous results, as evidenced, for example, by the recent tragedies involving defective commercial jets determined to be safe by their manufacturer,

Boeing, with little government oversight. *See, e.g.*, Natalie Kitroeff et al., *The Roots of Boeing's 737 Max Crisis: A Regulator Relaxes Its Oversight* (July 27 2019), https://www.nytimes.com/2019/07/27/business/boeing-737-max-faa.html (explaining that, prior to a series of crashes involving Boeing's planes, the Federal Aviation Administration "handed nearly complete control to Boeing," "effectively neuter[ing] the oversight authority of the agency").[1] This type of regime is particularly dangerous where, as here, safety decisions are made in secret, with no notice to the agency that is purportedly in charge.

Nor can FDA's enforcement authority save the GRAS Rule, because the Rule's provision for *secret* GRAS determinations renders that enforcement authority impotent. FDA cannot bring an enforcement action against an unknown company adding an unknown substance to unknown food. In fact, FDA is unlikely to discover violations of the FFDCA before injury occurs.

Nothing prevents FDA from designing a GRAS system that ensures FDA has the information necessary to fulfill its statutory duties. FDA's claims to the contrary rest on two faulty assumptions. First, FDA mistakenly assumes that Plaintiffs demand premarket *approval* of manufacturers' GRAS determinations when, in fact, Plaintiffs merely maintain that FDA must receive premarket *notice* of those determinations. FDA does not explain why it cannot require manufacturers to provide notice of GRAS determinations. Second, FDA relies extensively on a decades-old policy statement asserting that it would be impracticable to list all GRAS substances. But FDA misconstrues this statement, which refers only to the impracticability of listing all substances found to be safe through common use in food throughout history until 1958.

[1] This Court may take judicial notice of facts published in newspaper articles. *See* Fed. R. Evid. 201(b), (c)(2); *see also Wash. Post v. Robinson*, 935 F.2d 282, 291 (D.C. Cir. 1991) (taking judicial notice of newspaper articles).

FDA fails to explain (and the record does not show) why it cannot keep a running list of novel substances determined to be GRAS through scientific procedures *after* 1958.

Finally, FDA's argument that the optional notice system is the most efficient use of its resources is unfounded and illogical. It is not "efficient" for FDA to remain in the dark about substances added to food. To the contrary, FDA's ignorance threatens food safety and prevents the Agency from carrying out its statutory and constitutional responsibilities.

In sum, and for the reasons below, the GRAS Rule constitutes an unlawful subdelegation of FDA's authority, conflicts with the text and purpose of the FFDCA, and is arbitrary, capricious, and unreasonable. This Court should therefore grant Plaintiffs' Motion for Summary Judgment, deny FDA's Cross Motion for Summary Judgment, and vacate the GRAS Rule.

STATUTORY AND REGULATORY FRAMEWORK

When Congress adopted the Food Additives Amendment ("FAA") to the FFDCA in 1958, it created two categories of GRAS substances that are exempt from the premarket safety review process for food additives. First, Congress recognized that, "in the case of a substance used in food prior to January 1, 1958," GRAS status would attach if the substance was shown to be safe either through "scientific procedures" or through "experience based on common use in food." 21 U.S.C. § 321(s). Second—anticipating a future in which manufacturers would significantly alter common ingredients and create new substances using modern scientific techniques—Congress determined that any substance without a track record of safe use in food before 1958 could qualify as GRAS only if it was "generally recognized, among experts qualified by scientific training and experience to evaluate its safety, as having been adequately shown through scientific procedures . . . to be safe under the conditions of its intended use[.]" *Id*.

The new law mandated an entirely new approach to ensuring food safety and, as a result, caused some confusion among manufacturers and consumers. Accordingly, even before the FAA took full effect, FDA issued a regulation setting forth a list of substances known to be safe ("GRAS list"). *See* Substances that are Generally Recognized as Safe, 24 Fed. Reg. 9368 (Nov. 20, 1959) (codified as amended at 21 C.F.R. pt. 182). FDA explained that "[i]t is impracticable to list all substances that are generally recognized as safe for their intended use. However, by way of illustration, the Commissioner regards such common food ingredients as salt, pepper, sugar, vinegar, baking powder, and monosodium glutamate as safe for their intended use." 24 Fed. Reg. at 9368 (codified at 21 C.F.R. § 182.1). As the timing of this statement and the examples provided make clear, FDA's "impracticability" determination referred to listing all substances that qualify as GRAS based on pre-1958 "common use in food." FDA did not immediately establish procedures or standards for determining the GRAS status of new substances or new uses of GRAS substances. *See* FDA, *FDA's Approach to the GRAS Provision: A History of Processes* (Apr. 2006), https://www.fda.gov/food/generally-recognized-safe-gras/fdas-approach-gras-provision-history-processes#affirm, a PDF copy of which is attached as Exhibit A ("FDA's History"). Instead, the Agency determined the status of particular substances by ruling on food additive petitions and issuing opinion letters clarifying GRAS status. *See* Food Additive Status Opinion Letters; Statement of Policy, 35 Fed. Reg. 5810 (Apr. 9, 1970).

In 1969, in response to concerns that certain purportedly GRAS substances were carcinogenic, President Nixon directed FDA to "reevaluate *all items* generally recognized as safe for their intended use and used in food without food additive clearance." Eligibility of Substances for Classification as Generally Recognized as Safe in Food, 36 Fed. Reg. 12,093, 12,093 (June 25, 1971) (emphasis added). This spurred a twelve-year process in which the Select

Committee on GRAS Substances ("SCOGS") reviewed and evaluated substances on the GRAS list, using then-current scientific standards. *See* Eligibility of Substances for Classification as Generally Recognized as Safe in Food, 35 Fed. Reg. 18,623 (Dec. 8, 1970). FDA's initial foray into establishing procedures for external experts to use in determining GRAS status was related to the SCOGS's GRAS list review. *See* FDA's History at 4 (citing 35 Fed. Reg. 18,623).

In connection with this process, in 1971, FDA developed a mechanism—the GRAS affirmation petition process—that allowed manufacturers to petition FDA to affirm the GRAS status of substances that FDA did not review on its own initiative. FDA advised manufacturers that affirmation petitions must include "all relevant usage and safety data" for the substance in question. 36 Fed. Reg. at 12,094. In addition, FDA established clear limits for GRAS determinations, warning that novel substances are ineligible for GRAS status and determinations of safety based on scientific procedures, as opposed to pre-1958 common use, demand close scrutiny. *See id*. (explaining that FDA will provide notice and an opportunity for comment *before* affirming as GRAS substances developed or modified using modern science).

Just as manufacturers had sought assurance by submitting food additive petitions and requesting opinion letters in the years following the FAA's enactment, they continued to seek FDA approval by submitting food additive petitions and, if appropriate, GRAS affirmation petitions throughout the 1970s, 1980s, and early 1990s. *See* AR 008253. But this practice changed dramatically after 1997, when FDA implemented the "optional notice" provision in the proposed GRAS Rule (well before that Rule was finalized). Under the optional notice regime, the number of food additive petitions has dropped substantially, while GRAS determinations have increased. For example, from 2003-2013, FDA received 14 *optional* GRAS notifications (a subset of all GRAS determinations that manufacturers made during that time period) for every

food additive petition it received. AR 002604. In 2013 alone, FDA received at least 42 *optional* GRAS notifications but only one food additive petition. AR 002605. While it is clear that GRAS determinations now significantly outnumber food additive petitions, it is impossible to know exactly how many substances manufactures have *secretly* self-certified as GRAS without providing any notice to FDA. *See id*.

ARGUMENT

I. THE GRAS RULE CONSTITUTES AN UNLAWFUL SUBDELEGATION OF AGENCY AUTHORITY.

FDA maintains that the GRAS Rule does not impermissibly subdelegate its food safety responsibilities because the FFDCA neither expressly requires manufacturers to provide notice of GRAS determinations to FDA nor requires FDA to review GRAS determinations before purportedly GRAS substances enter the food system. *See* Defs.' Br. at 18. It also asserts that any subdelegation is permissible because the Agency retains enforcement power. *Id*. at 18–19. Further, FDA contends that the GRAS Rule does not insulate the Agency from accountability and judicial review otherwise available because the public has no right to compel FDA to determine whether a substance is a food additive. *Id.* None of these arguments has merit.

A. The GRAS Rule Is an Unauthorized Subdelegation to Food Manufacturers of a Core FFDCA Duty.

FDA agrees that subdelegations to outside, regulated parties are impermissible absent express statutory authorization. *See* Defs.' Br. at 17; Pls.' Br. at 9; *U.S. Telecom Ass'n v. FCC*, 359 F.3d 554, 566 (D.C. Cir. 2004) ("We therefore hold that [federal agencies] . . . may not subdelegate to outside entities—private or sovereign—absent affirmative evidence of authority to do so."); *accord Fund for Animals v. Kempthorne*, 538 F.3d 124, 132 (2d Cir. 2008). Moreover, FDA does not dispute that it lacks express authority under the FFDCA to subdelegate its duties to outside parties. *See* Defs.' Br. at 17–18. Thus, the GRAS Rule is unlawful.

FDA tries to recast the GRAS Rule's system of allowing manufacturers to make secret GRAS determinations as a permissible type of public-private arrangement that is not a "subdelegation." Defs.' Br. at 18. Yet FDA fails to acknowledge that, for agency reliance on private parties to be something other than a "subdelegation," the arrangement must fit one of the three types of "legitimate outside party input into agency decision-making processes" recognized by the courts and discussed in Plaintiffs' Opening Brief at page 14.[2] FDA has not made—and cannot make—the GRAS Rule fit within any of these three exemptions.

Seeking to avoid the inexorable conclusion that the GRAS Rule constitutes an unlawful subdelegation, FDA invokes one of two independent Second Circuit tests set forth in *Fund for Animals* for determining whether a subdelegation is permissible. *See* Defs.' Br. at 18 (citing 538 F.3d at 133).[3] But FDA misrepresents this test by asserting that an unlawful subdelegation occurs only when an agency allows an outside party to "make the 'entire determination of whether a specific statutory requirement has been satisfied.'" Defs.' Br. at 18 (citing *Fund for Animals*, 538 F.3d at 133) (internal citations and alterations omitted). The Second Circuit has not set such a high bar. Instead, this Circuit holds that an unlawful subdelegation occurs when an agency "shifts to another party *almost* the entire determination of whether a specific statutory

[2] These three exceptions are: (1) where the agency permissibly "condition[s] a grant of permission on the decision of another entity," (2) where an agency relies on the private party for factual information while retaining sufficient oversight over the final decision, and (3) where an agency seeks "advice and policy recommendations" from an outside party. *See* Pls.' Br. at 14 (citing *U.S. Telecom Ass'n*, 359 F.3d at 566).

[3] FDA misstates the function of the Second Circuit tests as asking whether a "subdelegation" has occurred at all, rather than evaluating whether a subdelegation is permissible. *Compare* Defs.' Br. at 18 ("But a 'subdelegation' only occurs when . . . ."); *id.* at 20 ("FDA's exercise of that discretion does not 'subdelegate' authority . . . .") *to Cooling Water Intake Structure Coal. v. EPA*, 905 F.3d 49, 79 (2d Cir. 2018) ("*Cooling Water*") ("An agency *impermissibly* delegates its authority where, without statutory authorization, 'it shifts to another party almost the entire determination of whether a specific statutory requirement . . . has been satisfied, or where [it] abdicates its final reviewing authority.'") (emphasis added).

requirement . . . has been satisfied." *Fund for Animals*, 538 F.3d at 133 (citation omitted) (emphasis added); *accord Cooling Water*, 905 F.3d at 79. FDA's omission of the word "almost" creates the misleading impression that the *entire* statutory determination must be handed to outside parties for the subdelegation to be impermissible; that is not the case.

FDA offers two theories for why the GRAS Rule is permissible under the first *Fund for Animals* test. First, the Agency argues that the FFDCA does "not impose mandatory GRAS notification on manufacturers or require FDA to review industry conclusions in advance of marketing," Defs.' Br. at 18, so there is nothing to subdelegate. But the FFDCA imposes other relevant duties. To ensure the safety of food, FDA must be able to police the boundary between food additives and GRAS substances, which requires that FDA at least receive notice of self-certified GRAS determinations. *See* Pub. L. No. 85-929, 72 Stat. 1748; 21 U.S.C. § 393(b) (delegating to FDA the responsibility of protecting the public health by ensuring that foods are safe); *see also* 21 U.S.C. § 348(c). The GRAS Rule, however, leaves this policing to self-interested outside parties.

Next, FDA argues that the GRAS Rule's reliance on outside parties is permissible because the Agency maintains its enforcement authority. *See* Defs.' Br. at 19. However, any enforcement necessarily would come after a violation has occurred and thus after "almost the entire determination" of whether a substance is safe to add to food already has been made.

Compounding its erroneous subdelegation analysis, FDA completely ignores the Second Circuit's second, independent test for determining whether an unlawful subdelegation has occurred. Under this test, an agency subdelegates authority when it abdicates "final reviewing authority," or pre-violation oversight. *Fund for Animals*, 538 F.3d at 133 (citing *Nat'l Park & Conservation Ass'n v. Stanton*, 54 F. Supp. 2d 7, 19 (D.D.C. 1999) ("The relevant inquiry . . .

becomes whether, in delegating its responsibility . . . [the agency] retained sufficient final reviewing authority . . . to *prevent a violation* of the unlawful delegation doctrine.") (emphasis added)). In *Fund for Animals*, the court upheld an order under which the Fish and Wildlife Service ("FWS") gave local agencies the ability to control cormorants, despite Congress's entrusting the birds to FWS. *Id*. at 126. The court premised its approval on the existence of pre-violation oversight mechanisms, including: 1) notification to FWS indicating the agencies' general intent to act; 2) notification thirty days in advance of any single action; and 3) annual reports describing parties' activities under the rule. *See Fund for Animals*, 538 F.3d at 130. With this information, FWS could act *before* a violation occurred. *See id*; *see also Cooling Water*, 905 F.3d at 80 (finding that EPA retained oversight, citing 79 Fed. Reg. 48,300 , 48,382 (Aug. 15, 2014) (EPA's oversight authority included the ability to conduct "a full vetting of information and concerns" prior to permit issuance and to "use the full extent of its [statutory] authority to object to . . . a permit" before it is issued)). Retaining pre-violation oversight is thus essential to *lawful* subdelegation.

The GRAS Rule contains none of the hallmarks of timely oversight the Second Circuit requires. Unlike in *Fund for Animals*, private entities acting under the GRAS Rule are not required to notify FDA of GRAS determinations or to submit reports to keep FDA informed. Unlike in *Cooling Water*, FDA cannot object to private entities' decisions before they are made because GRAS determinations may be kept secret by manufacturers. Indeed, the Government Accountability Office ("GAO") found that, "[o]nce a GRAS substance has entered the marketplace, FDA would find it difficult to identify that substance as the potential source of a food safety problem, especially if FDA is unaware that the substance has been determined to be GRAS." AR 008485.

Instead of explaining how the GRAS Rule meets the pre-violation oversight requirement, FDA leans on its after-the-fact enforcement authority. *See* Defs.' Br. at 19 (The Agency "has not surrendered or abdicated its enforcement authority . . . ."). But this ignores the Second Circuit's rule that *pre*-violation oversight is fundamentally distinct from *post*-violation enforcement. *See Fund for Animals*, 538 F.3d at 130; *Cooling Water*, 905 F.3d at 80; *see also U.S. Telecom Ass'n*, 359 F.3d at 568 (stating that "vague or inadequate assertions of final reviewing authority [will not] save an unlawful subdelegation") (citation omitted).

In sum, the GRAS Rule fails both of the Second Circuit tests for permissible subdelegation. Therefore, it cannot stand.

B. The GRAS Rule's Subdelegation Insulates FDA from Accountability and Judicial Review.

In addition to misstating and misapplying the tests for permissible subdelegation, FDA makes much of its belief that "Plaintiffs did not identify the putative constitutional basis of their subdelegation claims." Defs.' Br. at 17. However, it is well-settled that subdelegation claims are anchored both in agencies' constitutionally-granted powers to act and in courts' interpretations of separation of powers principles that enable the administrative state. *See, e.g.*, 16 C.J.S. Constitutional Law § 449 (discussing constitutional questions arising from the modern administrative state and delegations of authority). This Circuit has long recognized that subdelegation claims raise constitutional questions. *See R.H. Johnson & Co. v. SEC*, 198 F.2d 690, 695 (2d Cir. 1952), *cert. denied*, 344 U.S. 855 (1952) (holding that SEC did not unconstitutionally delegate to an outside party, because it retained oversight powers).

The GRAS Rule raises such constitutional questions because it insulates FDA from accountability for critical food safety determinations, while also eliminating the opportunity for judicial review of those determinations. *See* Pls.' Br. at 12. In response to this simple fact, FDA

offers only the non-sequitur that citizens cannot "force FDA to determine whether a substance is a 'food additive' so as to create a final agency action that may be challenged in court." Defs.' Br. at 20. FDA fails to address Plaintiffs' arguments or explain how the Agency maintains accountability for food safety decisions made in secret by entities plagued by conflicts of interest. *See* Pls.' Br. at 13.[4] FDA also does not address the erosion of judicial review inherent in a system that allows private actors to determine whether substances are GRAS or food additives: if GRAS determinations are made in error, the public is denied judicial remedies that would have been available under the procedures set forth in the FFDCA had those substances been properly denominated as food additives. And because secret GRAS determinations are not "agency actions" within the meaning of the APA, the public cannot challenge these decisions in court. Pls.' Br. at 12. Depriving the judicial branch of its role in reviewing actions that Congress delegated to the executive branch under the FFDCA violates separation of power principles.

II. THE GRAS RULE CONFLICTS WITH THE FFDCA AND THE APA.

Not only are FDA's arguments about subdelegation without merit, so too are its claims that the GRAS Rule complies with the FFDCA and the APA. *First*, FDA attempts to speed past the first step of analysis set out in *Chevron, U.S.A., Inc. v. Natural Resources Defense Council*, 467 U.S. 837, 942 (1984) ("*Chevron*"), by asserting that the FFDCA does not expressly indicate whether manufacturers must notify FDA of their GRAS determinations or preserve relevant records. *See* Defs.' Br. at 10. In so doing, FDA ignores relevant provisions of the FFDCA, which expressly require FDA to ensure the safety of food, verify the safety of new food additives, and

[4] FDA fails to address the effects of conflicts of interest on the permissibility of this subdelegation. *See* Pls.' Br. 13–14; *see also Sierra Club v. Sigler*, 695 F.2d 957, 962 n.3 (5th Cir. 1983) ("[A]n agency may not delegate its public duties to private entities . . . particularly private entities whose objectivity may be questioned on grounds of conflict of interest.").

evaluate the cumulative effects of food additives in combination with chemically- or pharmacologically- related GRAS substances. *Second*, FDA seeks to claim deference at *Chevron* step two by arguing that its decision to allow manufacturers to reach GRAS determinations in secret reflects a reasonable construction of the FFDCA. *See id*. at 12. But FDA cannot reconcile the GRAS Rule's provision for secret, potentially flawed GRAS determinations with that Act, which exists "to protect the health and safety of the public at large." *POM Wonderful, LLC v. Coca-Cola Co.*, 134 S. Ct. 2228, 2234 (2014). And *third*, FDA fails to sufficiently address Plaintiffs' claims that the GRAS Rule ignores an important aspect of the problem and conflicts with record evidence, rendering the Rule arbitrary and capricious under *Motor Vehicle Manufacturers Association v. State Farm Mutual Automobile Insurance Company*, 463 U.S. 29 (1983) ("*State Farm*"). For these reasons, the GRAS Rule is unlawful.

A. The GRAS Rule Prevents FDA from Complying with the FFDCA's Unambiguous Mandates.

FDA advances an impermissibly narrow view of judicial review under *Chevron* step one. Determining whether Congress has "directly spoken" to an issue requires more than simply checking to see if any provision of the governing statute expressly precludes an agency's action. *See Chevron*, 467 U.S. at 942. Courts "construe statutes, not isolated provisions." *King v. Burwell*, 135 S. Ct. 2480, 2489 (2015) (internal quotation marks omitted); *cf. Catskill Mountains Chapter of Trout Unlimited, Inc., v. EPA*, 846 F.3d 492, 508–520 (2d Cir. 2017) ("*Catskill*") (devoting a dozen pages to *Chevron* step one, including analyses of statutory text, structure, purpose, and legislative history). Thus, this Court must consider relevant provisions of the FFDCA "in their context and with a view to their place in the overall statutory scheme." *FDA v. Brown & Williamson Tobacco Corp.*, 529 U.S. 120, 133 (2000) (internal quotation marks omitted).

Applying the proper framework, it is clear that the GRAS Rule conflicts with the plain language, context, and purpose of at least three statutory mandates. *First*, the FFDCA unambiguously requires FDA to "protect the public health by ensuring that . . . foods are safe," a responsibility that FDA abdicates by allowing manufacturers to add substances to food in secret without agency oversight. 21 U.S.C. § 393(b)(2)(A). *Second*, the Act unambiguously requires FDA to adhere to a rigorous pre-market review process for food additives, *see id.* § 348(c), a duty that FDA "cannot intelligently and rationally perform . . . unless it determines what products are 'food additives' . . . and what products, because of their GRAS status, are exempt from regulation." *Se. Minerals, Inc. v. Harris*, 622 F.2d 758, 767 (5th Cir. 1980). And, *third*, the Act unambiguously requires FDA to evaluate the "cumulative effect of [each new food] additive in the diet of man or animals, taking into account any chemically- or pharmacologically- related substance or substances in such diet," 21 U.S.C. § 348(c)(5)(B), a task that FDA cannot complete if it is unaware of substances that enter food through manufacturers' secret GRAS determinations. Because FDA fails to grapple with these provisions, each of which directly and logically precludes the GRAS Rule, the Agency's *Chevron* step one analysis is unavailing.

1. <u>The GRAS Rule Prevents FDA from Complying with the FFDCA's Unambiguous Mandate to Ensure Food Safety.</u>

FDA defends the GRAS Rule by arguing that it "allow[s] the [A]gency 'to evaluate more, and higher priority substances.'" Defs.' Br. at 11 (quoting 81 Fed. Reg. at 54,961). But FDA cannot for efficiency's sake disregard the FFDCA's unambiguous mandate to "protect the public health by *ensuring* that . . . foods are safe," 21 U.S.C. § 393(b)(2)(A) (emphasis added). *See Brown & Williamson Tobacco Corp.*, 529 U.S. at 125 (noting that an agency "may not exercise its authority in a manner that is inconsistent with the administrative structure that Congress enacted into law") (internal quotation marks omitted). Nor can FDA ignore this mandate, even if

the Agency is correct in asserting that the Act's terms are "general and flexible." Defs.' Br. at 11; *see also Waterkeeper All. v. EPA*, 399 F.3d 486, 499 (2d Cir. 2005) (explaining that Congress's use of the verb "ensure" imposes oversight obligations). FDA cannot ensure food safety if it does not have complete, accurate information about substances added to food. *See* Pls.' Br. at 17–19.

Moreover, FDA's view that the GRAS Rule promotes efficiency defies common sense. By authorizing secret GRAS determinations, the GRAS Rule *hampers* FDA's ability to identify and evaluate high-priority substances. Manufacturers might choose to keep secret—and, therefore, FDA might know nothing about—the GRAS determinations that pose the greatest risk to public health. Adopting a GRAS Rule that requires manufacturers to provide FDA with notice of GRAS determinations would not deter the Agency from evaluating high-priority substances. To the contrary, as FDA has acknowledged, receiving information about manufacturers' GRAS determinations would "provide *additional* food safety protection and would allow FDA to be more fully informed about food in the marketplace." AR 008492 (emphasis added).

2. The GRAS Rule Impedes FDA's Ability to Fulfill Its Undisputed Duty to Conduct Premarket Review of "Food Additives."

FDA's argument about the plain meaning of the FFDCA does not account for the statutory context in which the GRAS exception appears. Courts "construe statutes, not isolated provisions." *King v. Burwell*, 135 S. Ct. 2480, 2489 (2015). Here, the statute makes clear that the GRAS Rule is illegal. Congress introduced the GRAS exception in 1958 as part of the Food Additives Amendment to the FFDCA, which was designed to correct the then-existing, dangerously inadequate system of addressing public health crises caused by unsafe substances in food only after those crises occur. *See* S. Rep. No. 2422, at 2 (1958). The FFDCA establishes an unambiguous presumption that food additives are *unsafe* for use in food, pending rigorous analysis by FDA. *See* 21 U.S.C. § 348(a). GRAS substances are excused from this analysis only

because they are, by definition, already "*generally recognized* . . . to be safe." *See id.* § 321(s) (emphasis added).

The GRAS Rule turns this statutory context on its head, introducing a system in which FDA cannot independently evaluate whether a substance is GRAS or a food additive, *see Se. Minerals, Inc.*, 622 F.2d at 767,[5] thereby gutting the FFDCA's mandatory provisions for pre-market review of food additives and undermining the Act's precautionary purpose. Under the GRAS Rule, FDA has no way of knowing whether a manufacturer has designated as GRAS a substance that should have been subject to the FFDCA's food additive approval process. As a result, FDA cannot prevent manufacturers from adding potentially dangerous substances to food.

3. The GRAS Rule Contravenes the FFDCA by Preventing FDA from Considering the Cumulative Health Effects of Food Additives.

FDA acknowledges that the FFDCA directs it to evaluate the "cumulative effect of [each new food] additive in the diet of man or animals, taking into account any chemically- or pharmacologically- related substance or substances in such diet." Defs.' Br. at 11–12 (quoting 21 U.S.C. § 348(c)(5)(B)). But the Agency does not even attempt to reconcile this unambiguous statutory command with the GRAS Rule's provision allowing manufacturers to add substances to food in secret. Instead, FDA asserts *first*, that the cumulative effects provision cannot be "sensibly read" to require FDA to develop a list of GRAS substances that might interact with

[5] FDA apparently understands *Southeastern Minerals, Inc. v. Harris* only to confirm the Agency's *authority* to distinguish between GRAS substances and food additives. *See* Defs.' Br. at 14 (citing *Se. Minerals, Inc.*, 622 F.2d at 767). In fact, the *Southeastern Minerals* court went to great lengths to reprimand FDA for failing to exercise this authority proactively and, instead, relying on its enforcement power to address the longstanding, unlawful use of a food additive. *See Se. Minerals, Inc.*, 622 F.2d at 767. As the court explained, FDA's failure to resolve the legal status of the substance in question "succeeded only in 'creat[ing] delay where in the interest of public health there should [have been] prompt action." *Id.* (quoting *Weinberger v. Hynson, Westcott & Dunning, Inc.*, 412 U.S. 609, 625 (1973)).

food additives, *id*. at 12, and *second*, that FDA has authority to decide how best to determine whether food additives might cause harm in combination with chemically- or pharmacologically-related substances. *See id*. Neither assertion explains how the GRAS Rule complies with the FFDCA's cumulative effects provision, which it does not.

FDA's reliance on a sixty-year-old regulation stating that it is "impracticable" to list all GRAS substances, Defs.' Br. at 12 (citing 21 C.F.R. § 182.1(a)), is unavailing. Even if FDA could not list all GRAS substances in existence when that regulation was enacted in 1959, it does not follow that FDA could not have begun to track new, science-based GRAS determinations from that point forward. Moreover, FDA does not explain why the Agency cannot identify substances subject to science-based GRAS determinations now.[6]

To the extent that FDA interprets its regulation to excuse compliance with the FFDCA, that interpretation is unlawful—even if it is longstanding. *See, e.g.*, *Wilderness Soc'y v. Morton*, 479 F.2d 842, 865 (D.C. Cir. 1973) (refusing to defer to an agency's decades-old policy of granting rights-of-way inconsistent with unambiguous statutory restrictions and rejecting "the proposition that administrative agencies are entitled to violate the law if they do it often enough"); *cf. F.J. Vollmer Co. v. Magaw*, 102 F.3d 591, 598 (D.C. Cir. 1996) ("[W]e do not see how merely applying an unreasonable statutory interpretation for several years can transform it into a reasonable interpretation.").

[6] FDA's failure to explain its inability to track GRAS substances is especially glaring given that FDA and other government agencies charged with protecting public health maintain similarly comprehensive lists. *See, e.g.*, 21 C.F.R. pt. 172 (listing approved food additives); *see also* EPA, *EPA Releases First Major Update to Chemicals List in 40 Years* (Feb. 19, 2019), https://www.epa.gov/newsreleases/epa-releases-first-major-update-chemicals-list-40-years (announcing EPA's completion of an inventory cataloguing all 40,655 chemicals actively being manufactured, processed, and imported in the United States).

In addition, FDA has not shown how it is even possible to implement the FFDCA's cumulative effects provision in light of the secrecy allowed under the GRAS Rule. Thus, FDA's bald assertion that it has authority to determine how best to implement the cumulative effects provision is non-responsive. The issue is not FDA's authority, but rather whether the GRAS Rule actually does what it claims to do. FDA does not and cannot demonstrate that it can implement the cumulative effects mandate of the FFDCA while allowing secret GRAS determinations.[7]

***

In sum, FDA's attempt to disregard the first step of *Chevron* fails. The FFDCA sets forth specific and unambiguous requirements to ensure food safety, to distinguish between food additives and GRAS substances, and to consider cumulative health effects. The GRAS Rule directly conflicts with those requirements and is therefore unlawful.

B. Even if the FFDCA were Silent or Ambiguous, the GRAS Rule is an Impermissible Construction of that Statute, and FDA's Arguments to the Contrary Are Unavailing.

Even if the FFDCA did not directly prohibit FDA from allowing manufacturers to add substances to food through secret GRAS determinations, the GRAS Rule still would fail because it does not reflect a permissible construction of the FFDCA, but instead is "arbitrary, capricious, [and] manifestly contrary to the statute." *See Chevron*, 467 U.S. at 843–44. Although FDA characterizes the second step of the *Chevron* analysis as "highly deferential," Defs.' Br. at 9, 12, that deference has limits. At *Chevron* step two, courts will defer to an agency's interpretation

[7] Amicus Curiae Safe Food Ingredients Coalition's ("SFIC") reliance on *Whitman v. American Trucking Associations, Inc.*, 531 U.S. 457 (2001), is unavailing. *See* Brief for SFIC as Amicus Curiae at 4-7. In that case, the Supreme Court held that Congress "unambiguously" did *not* intend for EPA to consider costs when setting national ambient air quality standards. By contrast, here, Congress unambiguously *required* FDA to consider the cumulative effects of chemically- or pharmacologically- related substances. *See* 21 U.S.C. § 348(c)(5)(B).

only if it is "supported by a reasoned explanation." *Catskill*, 846 F.3d at 521. "That is a requirement an agency can fail." *Kisor v. Wilkie*, 139 S. Ct. 2400, 2416 (2019). FDA fails here.

FDA argues that the GRAS Rule is reasonable because: (1) Congress did not specifically require FDA to review and approve GRAS substances before they are added to food, as it did with respect to food additives, *see* Defs.' Br. at 12; (2) FDA has determined that allowing secret GRAS determinations "constitutes the best use of [FDA's] resources," *id.*; and (3) FDA can address violations of the FFDCA, including situations in which manufacturers mistakenly (or intentionally) reach secret GRAS determinations about substances that are properly food additives, "on a case-by-case basis, [with] enforcement discretion." *Id*. at 14. These rationales are insufficient to rebut Plaintiffs' claim of illegal subdelegation, and they fare no better at *Chevron* step two.

First, FDA tries to make the GRAS Rule seem reasonable by positing that the only alternative to allowing secret GRAS determinations is requiring premarket approval. *See, e.g.*, Defs.' Br. at 12 ("FDA has reasonably determined that a voluntary notice submission regime for GRAS substances, rather than a preapproval process with mandatory submissions, constitutes the best use of its resources."). However, the universe of options for implementing the GRAS exception is not so narrow. For instance, GAO recommended that FDA improve its oversight of food safety not by mandating premarket approval, but by "requir[ing] any company that conducts a GRAS determination to provide FDA with basic information . . . such as the substance's identity and intended uses." AR 008507. The Court need not direct FDA to implement the GRAS exception in any particular way but, instead, must hold that the GRAS Rule and the secret determinations it allows do not meet the FFDCA's statutory demands.

Second, FDA fails to provide a reasoned explanation for its assertion that the optional notice requirement improves efficiency. FDA argues that the GRAS Rule has helped the Agency to acquire some—but not all—information it needs to do its job. *See* Defs.' Br. at 13 (asserting that the GRAS Rule "incentiviz[es]" manufacturers to submit information about GRAS substances to FDA, thus "increasing" FDA's awareness about substances in our food supply). This is not a "reasoned explanation," *Catskill*, 846 F.3d at 521, for how the GRAS Rule improves efficiency; FDA could obtain *all* the information it needs by requiring manufacturers to submit notice of GRAS determinations.

Although FDA reports that it has received a larger-than-usual number of optional GRAS notices under the GRAS Rule, the Agency cannot evaluate whether the number of determinations made *without* optional notice has increased by an equal or greater amount, because FDA has no information about secret GRAS determinations. Even if manufacturers kept only a small number of determinations secret, those determinations could pose a serious threat to public health. And preventing serious threats to public health certainly must trump efficiency.[8]

Third, FDA's reliance on its enforcement authority to justify the GRAS Rule undermines the FFDCA's precautionary purpose and, therefore, reflects an impermissible construction of that statute. As FDA acknowledged in adopting the GRAS Rule, "[w]hen there are new uses of an added food substance without FDA's premarket engagement, presumably because . . . manufacturer[s] ha[ve] concluded that such . . . use[s are] GRAS, [FDA] has to react to the new uses after they emerge," which "can be challenging." 81 Fed. Reg. at 54,965. Challenging and ineffective enforcement is precisely the problem that Congress sought to prevent when it

[8] Nor has FDA explained why it would be *inefficient* to satisfy the FFDCA *and* streamline enforcement by requiring manufacturers to notify FDA of their GRAS determinations.

amended the FFDCA in 1958. Before then, the government could prohibit the use of unsafe additives only by *proving* that they were poisonous or deleterious—a process that "require[d] approximately 2 years or more of laboratory experiments with small animals," during which time manufacturers could continue to use the additives in food, posing "dangers to public health." *See, e.g.*, H.R. Rep. No. 2284 at 1–2 (1958). By invoking its enforcement authority to support the reasonableness of the GRAS Rule, FDA proposes a return to the dangerously inadequate system of addressing public health crises caused by unsafe substances in food only after those crises occur. This is unreasonable.

FDA's examples of proactive enforcement, *see* Defs.' Br. at 15, illustrate this very point. Although FDA sent "warning letters" to several manufacturers of caffeinated alcoholic drinks in 2010, *id.*, it did so only *after* "there [were] numerous reports of young people falling ill after drinking [caffeinated alcoholic drinks]," "[t]he drink[s] ha[d] . . . been blamed for several deaths," and "[s]everal states . . . banned the drinks on their own." [9] Abby Goodnough, *F.D.A. Issues Warning Over Alcoholic Energy Drinks*, N.Y. Times, (Nov. 17, 2010), https://www.nytimes.com/2010/11/18/us/18drinks.html.[10] Similarly, FDA's decision to challenge the GRAS status of silver-lined food wrapping occurred years after scientists determined that this wrapping raised safety concerns. *See, e.g.*, Alessandra Pezzuto et al., *Food Safety Concerns Deriving from the Use of Silver Based Food Packaging Materials*, 6 Frontiers in Microbiology 1 (2015). FDA's scattered attempts at post-market, *post-injury* enforcement fail to

[9] Meanwhile, caffeinated alcoholic drinks remain available. *See* CNN Wire, *Pabst Blue Ribbon Releasing Limited-Supply Spiked Coffee in 5 States* (July 6, 2019), https://wtkr.com/2019/07/06/pabst-blue-ribbon-releasing-limited-supply-spiked-coffee-in-5-states/.

[10] Because FDA introduced extra-record sources in its cross-motion for summary judgment, *see* Defs.' Br. at 15, 15 n.10, Plaintiffs may rely on extra-record sources to respond. *See, e.g.*, *Lands Council v. Powell*, 395 F.3d 1019, 1030 (9th Cir. 2005) (explaining that admission of extra-record evidence is permitted "if the agency has relied on documents not in the record").

establish that allowing manufacturers to add substances to food through secret GRAS determinations reflects a reasonable interpretation of FDA's statutory duty to "ensure" food safety. This is especially so considering that—as FDA acknowledges, *see* Defs.' Br. at 16—the GRAS Rule contains no recordkeeping requirements to ensure that industry is complying with the requirements in the statute. *See* Pls.' Br. at 18–19.

Finally, FDA cannot save the GRAS Rule by asserting that Congress has "implicitly ratified" it. *See* Defs.' Br. at 14. The cases upon which FDA relies are distinguishable. For instance, in *Barnhart v. Wilson*, 535 U.S. 212 (2002), the Court considered subsequent congressional activity concerning the *very issue* at stake in the litigation. *See* 535 U.S. at 220. Not so here. FDA fails to identify subsequent congressional action bearing on the meaning of the GRAS exception or FDA's statutory responsibilities. That omission is fatal. Courts are reluctant to "recognize congressional acquiescence to administrative interpretations," especially if Congress has not addressed the "precise issue" in question. *Solid Waste Agency v. U.S. Army Corps of Eng'rs*, 531 U.S. 159, 169, 169 n.5 (2001); *see Am. Civ. Liberties Union v. Clapper*, 785 F.3d 787, 819 (2d Cir. 2015) ("[I]n the case of an administrative interpretation of a statute,... the doctrine of legislative ratification [will] apply" only if "Congress has spoken clearly enough to constitute acceptance and approval of an administrative interpretation.") (internal quotation marks omitted). Amendments enacted *before* FDA proposed the GRAS Rule and affecting a different agency's oversight of different substances, *see* Defs.' Br. at 14 (citing the Food Quality Protection Act of 1996, Pub. L. 104-170, 110 Stat. 1489), do not amount to implicit ratification of that Rule.

C. The GRAS Rule is Arbitrary and Capricious, as It Fails to Consider Important Aspects of the Problem and is Contrary to the Record.

Not only does the GRAS Rule fail under *Chevron* steps one and two, it also cannot pass muster under the "stricter and more exacting review of the agency's rationale and decisionmaking process" set forth in *State Farm*. *Catskill*, 846 F.3d at 521. Under that test, which is distinct from the statutory construction analysis considered under the *Chevron* framework, agency action must be set aside if the agency fails to "examine[] the relevant data and articulate[] a satisfactory explanation for its action," or if the decision fails to "reveal a rational connection between the facts found and the choice made." *Nat. Res. Def. Council v. EPA*, 658 F.3d 200, 215 (2d Cir. 2011) (internal citations omitted). FDA's response to Plaintiffs' claims that the Agency ignored critical problems documented in the record fails this test.

FDA argues that it addressed the concerns raised in the GAO report "at length" and decided that the "voluntary" GRAS notice system sufficiently addressed those concerns. *See* Defs.' Br. at 17. However, as discussed *supra*, "efficiency"—especially an illogical and unjustified assertion of efficiency—does not justify an otherwise arbitrary rule. Nor does it provide a "satisfactory explanation" of FDA's choice to ignore the public health and safety concerns raised by the GAO. *Nat. Res. Def. Council*, 658 F.3d at 215. For these reasons, the GRAS Rule is arbitrary and capricious and cannot stand.

III. FDA FAILS TO REBUT PLAINTIFFS' ARGUMENTS THAT THE GRAS RULE'S CRITERIA FOR DETERMINING GRAS STATUS ARE ARBITRARY AND CAPRICIOUS.

Finally, FDA's defense of the GRAS Rule's criteria for determining GRAS status also misses the mark. FDA asserts that Plaintiffs can neither demonstrate that the FFDCA expressly precludes the GRAS Rule's criteria nor that those criteria reflect an unreasonable interpretation

of the FFDCA. *See* Defs.' Br. at 20. FDA is wrong. The GRAS Rule's criteria are both arbitrary and capricious and in conflict with the FFDCA in at least five ways.

First, the GRAS Rule's criteria fail to ensure that manufacturers base GRAS determinations on adequate data, information, and methods—in part, because the GRAS Rule authorizes manufacturers to rely on *unpublished* material corroborated by *unpublished* material. *See* Pls.' Br. at 21 (citing 21 C.F.R. § 170.30(b)). FDA asserts that because it requires GRAS determinations to reflect "common knowledge" and incorporate data that are "generally available and accepted," it does not matter whether the data or information relied on are published or unpublished. Defs.' Br. at 21 (quoting 21 C.F.R. § 170.30(b)). But this is inconsistent with FDA's own conclusion that *published* material is more likely to be objective, credible, and generally known. *See* 81 Fed. Reg. at 54,973.

Second, the GRAS Rule fails to include sufficient criteria to ensure that manufacturers' GRAS determinations are free from conflicts of interest. *See* Pls.' Br. at 22–23. Given FDA's admission that it "has long been aware of concerns about the possibility of conflicts on GRAS panels," Defs.' Br. at 22, the GRAS Rule's failure to protect against such conflicts runs counter to the evidence before the Agency and is, therefore, unlawful. *See State Farm*, 463 U.S. at 43. The failure to control conflicts is also unlawful because it undermines FDA's ability to ensure food safety and, thus, is inconsistent with the FFDCA. *See Chevron*, 467 U.S. at 842–43.

It is no defense to recite the GRAS Rule's statement that "[g]eneral recognition of safety requires common knowledge *throughout* the scientific community," s*ee* Defs.' Br. at 24 (emphasis in original), because the GRAS Rule does not *require* manufacturers to consult unbiased experts before reaching safety conclusions. And FDA's reliance on elements of the *optional* GRAS notice process is sorely misplaced, *see id.*, as manufacturers can avoid these

procedural hurdles simply by opting out of the process altogether. So too with FDA's non-binding draft guidance.[11] FDA's last-ditch argument that there *might* be some GRAS determinations untainted by conflict, *see* Defs.' Br. at 21 n.16, effectively concedes that conflicts are pervasive and, thus, serves only to demonstrative that the Agency ignored an important part of the problem in issuing the GRAS Rule without adequate criteria to prevent conflicts.

Third, it is patently unreasonable to allow manufacturers to determine a substance to be "generally recognized as safe" *after* FDA raises safety concerns about that substance. Despite FDA's assertion, *see* Defs.' Br. at 23, this is not a hypothetical problem; instead, the record reveals that manufacturers *already* have exploited this loophole to fast-track use of substances associated with fetal leukemia, dangerous allergic reactions, and other serious health problems. *See* Pls.' Br. at 6–7 (citing AR 008272–73). By adopting the GRAS Rule without adequate criteria to prevent manufacturers from ignoring FDA's own safety concerns and failing to engage with record evidence demonstrating that such criteria are necessary, FDA "entirely failed to consider an important aspect of the problem." *State Farm*, 463 U.S. at 43.

Fourth, FDA cannot defend the GRAS Rule's failure to ensure that manufacturers do not prematurely reach GRAS determinations about novel or newly synthesized substances that—by their very nature—cannot be "generally recognized as safe."[12] This failure runs afoul of the plain meaning and purpose of the FFDCA, rendering the Rule unlawful. FDA's assertion that Plaintiffs support the "arbitrar[y] impos[ition]" of rigid timelines, *see* Defs.' Br. at 23, is plainly untrue. Instead, Plaintiffs argue that the GRAS Rule is unlawful because it fails to constrain

[11] Although FDA warns that manufacturers who disregard its advice "do so at their own risk," Defs.' Br. at 24, the Agency does not explain how it intends to identify secret, inadequate GRAS determinations for enforcement.

[12] As FDA explained in 1971, "no substance will be eligible for GRAS status if it has no history of food use." 36 Fed. Reg. at 12,094.

manufacturers from issuing GRAS determinations under circumstances that *FDA itself* would consider inappropriate. *See, e.g.*, 81 Fed. Reg. at 54,976 (acknowledging that "the passage of time is relevant in an evaluation of whether a substance is GRAS under its conditions of intended use"); *id*. at 54,964 (explaining that certain novel and newly synthesized substances probably do not qualify for GRAS status, but instead "likely . . . warrant formal premarket review and approval by FDA").

Fifth, FDA twists itself in knots to avoid taking a position about whether carcinogenic substances can be GRAS and, in doing so, fails to address Plaintiffs' arguments. *See* Defs.' Br. at 23–25. Despite FDA's contentions to the contrary, Plaintiffs do not claim that the Delaney Clause "governs the determination of whether a substance is GRAS or a food additive." *Id*. at 24. Instead, Plaintiffs argue that if a substance cannot be deemed "safe" as a food additive, it certainly cannot qualify to be "generally recognized as safe." *See* 21 U.S.C. § 321(u) (explaining the meaning of the term "safe" as applied in 21 U.S.C. §§ 321(s) and 348); 21 C.F.R. § 570.30(b) ("General recognition of safety shall require the same quantity and quality of scientific evidence as is required to obtain approval of a food additive."). The GRAS Rule is illogical and unlawful because it allows manufacturers to secretly self-certify carcinogenic substances as GRAS, even though those substances could never be deemed "safe" as food additives. *See* 21 U.S.C. § 348(c)(3)(A) (expressly prohibiting FDA from approving carcinogenic substances as food additives).

CONCLUSION

For the reasons set forth above and in Plaintiffs' Motion for Summary Judgment, this Court should grant Plaintiffs' Motion, deny Defendants' Cross-Motion, and vacate the GRAS Rule.

August 23, 2019

Respectfully submitted,

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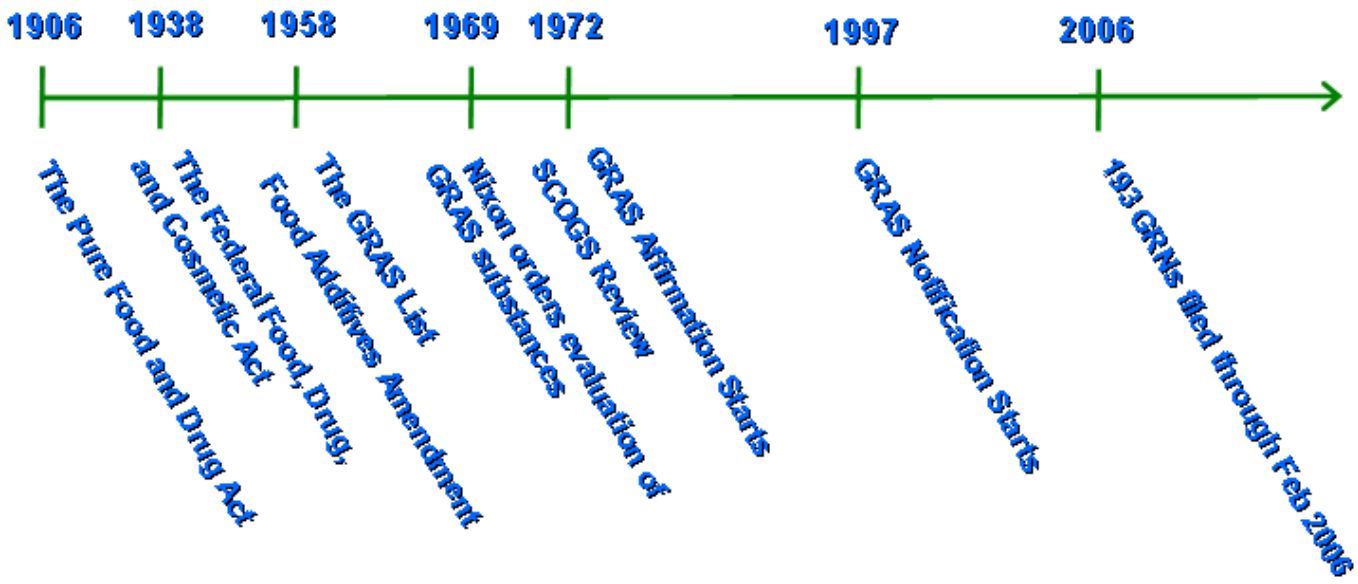
Exhibit A

FDA's Approach to the GRAS Provision: A History of Processes

Excerpted from Poster Presention at the FDA Science Forum - April 2006

Paulette M. Gaynor, Richard Bonnette, Edmundo Garcia, Jr., Linda S. Kahl, Luis G. Valerio, Jr.
Division of Biotechnology and GRAS Notice Review,
Office of Food Additive Safety (OFAS),
Center for Food Safety and Applied Nutrition, Food and Drug Administration

A GRAS Timeline



This picture is a graphical representation of a timeline starting in 1906 when the Pure Food and Drug Act was passed. Milestones along the way to the present include the 1938 Federal Food Drug and Cosmetic Act, and the Food Additives Amendment and the GRAS list in 1958. In 1969, President Nixon ordered an evaluation of GRAS substances and in 1972 the GRAS Affirmation process began. The GRAS Notification Program started in 1997 and by the end of 2006, 193 GRAS Notices were filed.

Abstract

Under the 1958 Food Additives Amendment to the Federal Food, Drug, and Cosmetic Act, any substance intentionally added to food is a food additive and is subject to pre-market approval by FDA unless the use of the substance is generally recognized as safe (GRAS; the GRAS provision) (or otherwise excepted from the definition of food additive - e.g., color additive). By 1961, FDA had amended its regulations to include a list of food substances that are GRAS under certain conditions of use ("the GRAS list"). During the 1960's, many manufacturers requested FDA's opinion on whether their conclusions of GRAS status were justified and received "opinion letters." In 1969, FDA removed cyclamate salts from its GRAS list as a result of safety questions, and then-President Nixon directed FDA to reexamine the safety of GRAS substances. In the 1970's, FDA announced that it was conducting a "comprehensive review" of presumed GRAS substances and established rulemaking procedures to affirm the GRAS status of substances that were either on the GRAS list or the subject of a petition ("GRAS affirmation"). To eliminate the resource-intensive rulemaking procedures, in 1997, FDA proposed to replace the GRAS affirmation petition process with a notification procedure ("GRAS notification").

Excerpts from Legislative History

"Proof of the pudding is in the eating" - Origins of Generally Recognized.

Mr. Dies (Texas Congressman): "I think that it [the concept of GRAS] is so vague and indefinite and general that it puts the manufacturer, the processor, in a very bad situation."

"So it seems to me the standard ought to be simplified and eliminate this thing of saying "generally recognized. If you go into the courthouse, who is an expert? How many would have to agree to be generally recognized?"

Mr. Larrick (FDA Commissioner): "Congressmen, all I can say is that we have used this language since 1938 and we have successfully handled over 10,000 new drug applications, and in my opinion the proof of the pudding is the eating."

From Commissioner Larrick's opening remarks

"We believe only those chemicals should be automatically exempted from the new law which are recognized among competent experts as safe for their intended use. This would make it unnecessary, for example, to do studies on table salt, but would not approve the continued use, without proof of safety, of the synthetic emulsifiers now widely used in some fabricated foods."

"The GRAS List"

- 1958 Food Additives Amendment: Congress recognized that many food substances would not require a formal premarket review by FDA to assure their safety, either because:
    - Their safety had been established by a long history of use in food; or

    - By virtue of the nature of the substances, their conditions of use, and the information generally available to scientists.
- Two-step definition of "food additive:"
    - Broadly includes any substance that becomes a component of food or otherwise affects the characteristics of food.
    - Excludes substances that are recognized, among qualified experts, as having been adequately shown through scientific procedures (or, in the case of a substance used in food prior to January 1, 1958, through experience based on common use in food) to be safe under the conditions of their intended use.
- December 9, 1958: FDA published a list of GRAS substances and incorporated the list in Title 21 of the Code of Federal Regulations. The current list appears in 21 CFR Parts 182, 184, and 186.

"Opinion Letters"

- Many substances that were considered GRAS by the food industry were not included in FDA's 1958 GRAS list.
- Many manufacturers wrote to FDA and requested an opinion letter in which an FDA official would render an informal opinion on the GRAS status of use of the substance
- Often available only to requestor
- Revoked in 1970 (21 CFR 170.6; 35 FR 5810; April 9, 1970)

"Comprehensive Review"

- October 30, 1969: President Nixon directed FDA to make a critical evaluation of the safety of GRAS food substances.
- March 28, 1972: - Life Sciences Research Office (LSRO) of the Federation of American Societies for Experimental Biology (FASEB) began its contract with FDA to summarize the available scientific literature and to recommend what restrictions, if any, on the use of the substances would be needed to ensure their safe use in food.
- 1970's: LSRO selected qualified scientists (designated as the Select Committee on GRAS Substances (SCOGS)) as consultants to review and evaluate the available information on each of the GRAS substances. The Select Committee's evaluations were made independently of FDA or any other group, governmental or nongovernmental.
- 1970's - 1980's: FDA made tentative reports from SCOGS available to the public and provided opportunity for the public to appear before the Select Committee at a public hearing. SCOGS considered the data, information, and views presented at the hearing in

developing its final reports. By 1982, SCOGS had submitted opinions to the FDA on the health aspects of more than 400 substances.

"GRAS Affirmation"

- 1972: FDA conducted rulemaking to establish the procedures (21 CFR 170.35) that it would use to affirm the GRAS status of substances that were the subject of the GRAS review. That rulemaking included a mechanism (the GRAS affirmation petition process) whereby an individual could petition FDA to review the GRAS status of substances not being considered as part of the agency's GRAS review.
- 1970's - 1980's: GRAS Affirmation based on the SCOGS Review
    - After receiving a final SCOGS report, FDA reviewed the report and related information
    - When appropriate, FDA issued a notice of proposed rulemaking to affirm GRAS status
    - If, after reviewing comments to the proposal, FDA concluded that the available data and information supported GRAS status, FDA issued a final rule affirming GRAS status by amending 21 CFR 184 (direct food ingredients) or 186 (indirect food substances).
      Examples: Gums, dextrans, various salts (e.g., sodium, potassium, calcium and iron salts),
- 1973 - 1997: GRAS Affirmation Petition Process
    - Industry submits GRAS Affirmation Petition
    - FDA publishes notice of filing and requests comment
    - When appropriate after considering comments, FDA issues a final rule affirming GRAS status
      Examples: Canola oil, enzyme preparations, whey, cocoa butter substitute

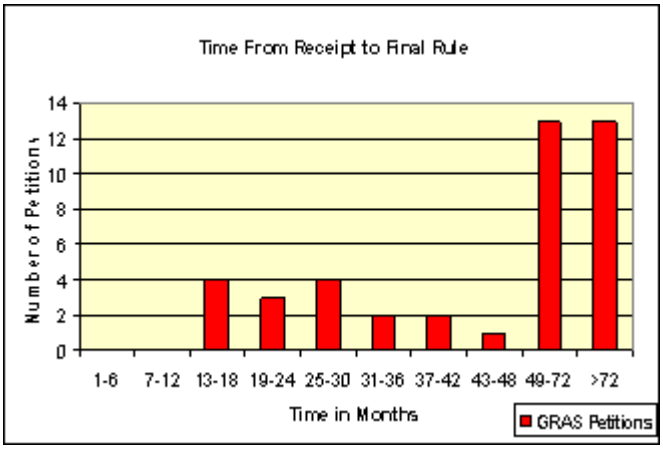
"GRAS Notification"

- April 17, 1997: FDA proposed to established a a notification procedure whereby a person may inform FDA of a determination that the use of a substance is GRAS (62 FR 18938; April 17, 1997).
    - Industry submits GRAS notice
    - FDA is evaluating whether each submitted notice provides a sufficient basis for a GRAS determination and whether information in the notice or otherwise available to FDA raises issues that lead the agency to question whether use of the substance is GRAS

- FDA is responding to the notifier by letter
  Examples: Phytosterols, DAG oil, enzyme preparations

GRAS Affirmation Petitions

Industry sponsored GRAS affirmation petitions completed from 1974 through August 1990. In general, industry sponsored GRAS affirmation petitions completed after that took >72 months. Approximately 20 percent of the substances in 21 CFR Part 184 are the result of industry petitions.



GRAS Notices

GRAS notices completed from 1998 through December 2005. The mean time to respond to these 177 notices is 162 days.