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GRAS from the ground up: Review of the Interim Pilot Program for GRAS notification

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ABSTRACT

After publication of the draft Generally Regarded As Safe (GRAS) rule in 1997, the United States (US) Food and Drug Administration (FDA) initiated an Interim Pilot Program encouraging the notification to FDA of GRAS determinations. This paper analyzes GRAS notifications submitted during the Interim Pilot Program along with warning letters issued during the same time period to better understand the evolution of the program and anticipate the future GRAS landscape. The success of the GRAS Notification program is demonstrated by the increasing rate of GRAS Notifications submitted to the FDA during the Interim Pilot Program, as well as the shift from a primarily domestic process to a process featuring an equal to greater contribution of GRAS Notifications from companies outside the US. Analysis of the first 600 GRAS Notifications revealed a number of interesting trends regarding the inclusion and composition of GRAS Expert Panels; differences in notifications for substances with nutritive, processing aid, or effect; and the duration of GRAS Notifications. The review of FDA warning letters associated with GRAS issues provides additional insight into GRAS notices, from the perspective of ongoing post-market emphasis on food safety with the implementation of the GRAS Final Rule.

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1. Introduction

1.1. History

The 1938 Food Drug and Cosmetic Act (FDCA) was amended by the 1958 Food Additive Amendment to define a food additive {§401(s)}[1] and to require premarket approval by the United States (US) Food and Drug Administration (FDA) for any new uses of food additives. Food substances that would be designated as Generally Regarded As Safe (GRAS) were exempted from both the "food additive" definition and the premarket approval process under the 1958 Food Additive Amendment, as the use of such substances could either be determined as safe based on long history of use in food, or the substance was of a nature and use with limited safety concern being substantiated by information readily available and recognized by the scientific community. The 1958 amendment included a list of GRAS substances (e.g., sugar and gelatin), which was again amended to include a more formal GRAS list in 1961. This list, as well as, additional substances evaluated by the Select Committee on GRAS Substances (SCOGS) prior to and as part of the GRAS affirmation process instituted in 1972 (21CFR170.35), can now be found within Title 21 of the Code of Federal Regulations as follows:

- 21CFR182 – Substances GRAS (e.g., hydrochloric acid, caffeine, caramel, biotin)

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[1] §401 "… (s) *The term "food additive" means any substance the intended use of which results or may reasonably be expected to result, directly or indirectly, in its becoming a component or otherwise affecting the characteristics of any food (including any substance intended for use in producing, manufacturing, packing, processing, preparing, treating, packaging, transporting, or holding food; and including any source of radiation intended for any such use), if such substance is not generally recognized, among experts qualified by scientific training and experience to evaluate its safety, as having been adequately shown through scientific procedures (or, in the case of a substance used in food prior to January 1, 1958, through either scientific procedures or experience based on common use in food) to be safe under the conditions of its intended use; …"*

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- o 21CFR184 – Direct food substances affirmed as GRAS (e.g., acetic acid, papain, sucrose)
- o 21CFR186 – Indirect food substances affirmed as GRAS (e.g., clay, dextrans, pulp)

On 17 April 1997, the FDA published a Proposed Rule outlining a voluntary GRAS Notification process and interim policy to replace the "resource intensive" GRAS affirmation petition process (United States Food and Drug Administration, 1997). Additional impetus for this program was due to the lengthy time period for review, that for those reviews conducted by FDA after 1990 was upwards of 72 months (United States Food and Drug Administration, 2006).

With this publication, FDA invited individuals to notify GRAS determinations to the Agency as part of an Interim Pilot Program. The safety standard for these notifications would be the responsibility and under the liability of the notifier, however the FDA would provide one of three possible outcomes for their review:

1. No Questions: The FDA has no questions upon completing their review regarding the GRAS status of the substance under the intended conditions of use
2. Withdrawn: At the notifier's request, the FDA has ceased to evaluate the GRAS Notification
3. No Basis: The GRAS Notification does not provide a sufficient basis to determine the substance is GRAS under the intended conditions of use

In addition to proposing a 90-day review period, the Proposed Rule announced the creation of a webpage to describe the FDA's inventory of GRAS notices (United States Food and Drug Administration, 2017a). This website provides the substance name, GRAS Notification (GRN) number assigned by FDA, the FDA letter sent in response to the notice, name and address of the notifier (the person making the GRAS determination), substance conditions of use, and the basis of the determination (whether by scientific process or history of use prior to 1958).

The first GRAS Notification filed as part of the Interim Pilot Program was on 10 February 1998 for soy isoflavone. As of 15 January 2017, 678 GRAS Notifications appear on the FDA notification website, representing 679 total outcomes (GRAS Notification #13 included two evaluations notified as a single submission to the agency). Of the 679 outcomes for these GRAS Notifications, the FDA has provided a "No Questions" response to 74% (505), 16% (110) were "Withdrawn", 3% (17) received a "No Basis" response, and 7% (47) are still pending FDA resolution (Fig. 1).

Due in part to mounting pressure from both external parties, such as that represented in the consent decree filed by the Center for Food Safety in 2014 (United States District Court, 2014) and internal pressures as specified in the GAO report 2010[2] (United States Government Accountability Office, 2010), the FDA released their Final GRAS Rule on 12 August 2016 (United States Food and Drug Administration, 2016b). The Final Rule emphasized two aspects of GRAS: 1) a group of experts must agree the food is safe; and 2) the food safety information must be common knowledge. In the Final Rule, FDA maintained the voluntary GRAS Notification program, including use of the GRAS Notification inventory provided on the US FDA website. In contrast to the Proposed Rule, the Final Rule allows 180 days for FDA to respond to a GRAS Notification, with the potential for a 90-day extension.

[2] "… FDA should strengthen its oversight of food ingredients determined to be Generally Recognized as Safe (GRAS) …"

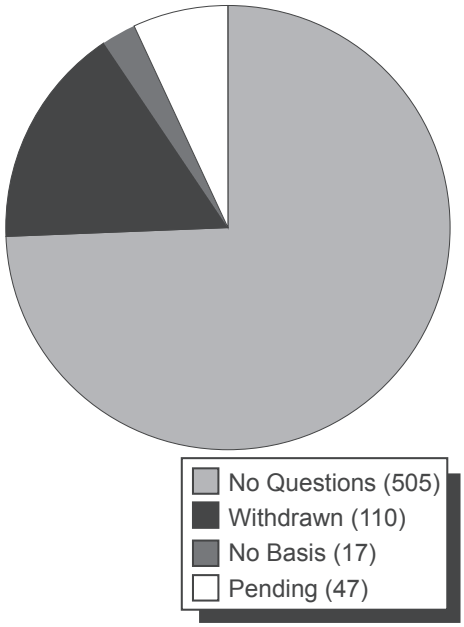

Fig. 1. GRAS Notification outcomes.

1.2. Process

The FDA has jurisdiction for more than 80% of the food in the US food supply (United States Food and Drug Administration, 2011), and the Center for Food Safety and Applied Nutrition (CFSAN) Office of Food Additive Safety reviews the safety of food ingredients and packaging. GRAS food ingredients are "generally recognized, among qualified experts, to be safe under the conditions of its intended use" (GRAS Final Rule 21CFR170.250(b)), and therefore do not require premarket approval by the FDA. FDA has defined safe as "reasonable certainty in the minds of competent scientists that the substance is not harmful under the conditions of its intended use" (GRAS Final Rule 21CFR170.3(i)).

Demonstration that a substance is GRAS requires scientific data: 1) that is generally known; and 2) the interpretation of which has consensus among qualified experts as to the safety for human consumption for the intended conditions of use. This is true for substances determined to be GRAS through scientific procedures (GRAS Final Rule 21CFR170.30(b)) and demonstrated to be GRAS through common use in food prior to 1 January 1958 (GRAS Final Rule 21CFR170.30(c)). Although not specifically required by the Final Rule, a Notifier may convene a panel of appropriate experts who have expertise demonstrated by training and experience (a GRAS Expert Panel) to review the safety of the substance and to satisfy the requirement for this safety being "common knowledge throughout the scientific community" (GRAS Final Rule 21CFR170.30(a)).

A GRAS determination based on common use in food is rarely used today and requires a substantial history of food consumption by many consumers before 1958. In fact, during the Interim Pilot Program, only 10 Notifications were sent to the FDA based on a common use in food. The most recent of these was filed in 2010 and only four of these 10 GRAS Notifications received a "No Questions" response from the FDA. Thus this mechanism is unlikely to represent a significant number of GRAS Notifications in the future.

In the Final Rule, the FDA clarifies the expectation for demonstrating the safety of a GRAS substance, using scientific procedures, is the same as that for a substance submitted to FDA as a Food Additive Petition (FAP); however, unlike a GRAS determination, the

FAP allows data that are considered proprietary and not publicly available to be considered as part of the safety review. In addition, as a FAP is an FDA approval process, FDA review is required prior to marketing of the substance for use in food (21CFR171.1). The Final Rule reiterates a pre-market review of GRAS substances is not required and the submission of a GRAS Notification is voluntary.

Although the Final Rule maintains that FDA notification of GRAS determinations is a voluntary process, as previously stated, over 600 GRAS determinations were notified to the FDA over the course of the Interim Pilot Program. The data presented in this paper indicates that the GRAS Notification program is likely to continue to be utilized extensively by food manufacturers.

1.3. Summary

This article provides a detailed analysis of the first 600 GRAS Notifications submitted to FDA during the Interim Pilot Program, as well as the associated warning letters mentioning GRAS during the last 10 + years (i.e., since 2005). The purpose of these analyses was to identify trends and insights into the history and evolution of the GRAS Notification program, as well as how the GRAS Notification program may evolve going forward in light of the publication of the Final Rule.

2. Methods

2.1. Analysis of FDA GRAS notifications

All information pertaining to the first 600 GRAS Notifications analyzed in this publication were extracted from the US FDA GRAS Notification Inventory (United States Food and Drug Administration, 2017a). For each GRAS Notification, the following information was collected (Supplemental Table 1):

- Notification number
- Filing date
- Date of closure
- Duration of resolution of the GRAS Notification
- Notification outcome (No Question, Withdrawn, No Basis)
- Basis for the GRAS conclusion (Scientific Procedures, Common Use in Foods)
- Name of the notifier
- Geographical region (North America, Europe, Asia, etc.)
- Country of the notifier (in cases where multiple are listed, this is the first country listed)
- Whether a GRAS Expert Panel was convened, and if so:
  - o How many individuals served on the Panel
  - o The names of the individuals (when available)
  - o Presence on the panel of the most prolific GRAS Experts (Table 5)
- Functional purpose of the substance (Nutritive, Processing Aid, Technical Effect)
- Whether the substance was included in one of five functional classes analyzed in further detail (Fats and Oils, Enzymes, Probiotics, Sweeteners, Carotenoids), and if so
  - o The Estimated Daily Intake (EDI) for these substances was included

For this publication, the first 600 GRAS Notifications (GRN #1 to 600), with 601 individual outcomes, were analyzed. GRN #13 had two outcomes considered as part of this analysis, as this GRAS Notification received two different responses for subsets of substances included in this single GRAS Notification. For the purposes of analysis, the GRAS Notifications were separated chronologically into groups of 100.

2.2. Definition and transformation of Estimated Daily Intake (EDI), as needed

The GRAS Final Rule requires inclusion of a dietary exposure, such as an Estimated Daily Intake (EDI) per 21CFR170.235 (GRAS Final Rule). However, since the format of the dietary exposure is not mandated, the EDIs reported in the first 600 GRAS Notifications were not standardized. To enable comparison between GRAS Notifications, the EDIs for specific notifications were adjusted to a standard unit of mg/kg/day for the 90th percentile, or highest maximum intake. When the GRAS Notification did not report the EDI in this specific format, the data were transformed as follows:

- Values expressed as mg/day were converted to mg/kg/day using the standard body weight value of 60 kg for an adult
- When a GRAS Notification covered more than one substance (e.g. a combination of fatty acids or carotenoids), the EDI used in this analysis represents a total of all substances
- Values for enzymes, when expressed as mg of Total Organic Solids (TOS) are represented in this chart as mg of substance per kg body weight
- Values for sweeteners, where appropriate, are provided as mg of steviol equivalents per kg body weight (but expressed as mg/kg in this analysis)

2.3. Analysis of GRAS Expert Panels

Determination of whether a GRAS Notification included a GRAS Expert Panel was based solely on if a GRAS Expert Panel was convened to support the specific GRAS Notification submitted to the FDA. GRAS Notifications that referenced a previously-convened GRAS Expert Panel, or other expert panel (e.g. JECFA) were not considered as GRAS Notifications having convened a GRAS Expert Panel.

2.4. Functional purposes of substances

All substances were categorized under one of three functional purposes:

Nutritive: Substances that provide value in sustaining human existence by such processes as promoting growth, replacing loss of essential nutrients, or providing energy (21CFR101.14(a)(3)) Examples include vitamins, minerals, fats, carbohydrates (including oligosaccharides), proteins, and probiotics. Essentially, any substances with an intended use that claimed a benefit for a nutritional purpose were included in this category (e.g., fats and oils, probiotics, carotenoids, oligosaccharides).

Processing aids: Substances added to food during processing but removed from the food before the product is in the finished form, substances converted into constituents normally present in the food that do not significantly increase the amount of the constituents normally present in the food, or substances present in the finished food at an insignificant level (meaning they do not have any technical or functional effect in the finished food) per 21CFR101.100(a)(3)(ii). The primary example of this functional category is food-processing enzymes.

Technical Effect: Substances that provide a physical or technical effect in the finished food (as opposed to processing aids without a technical function in the finished food) not necessary for, or do not provide a benefit to, the body's nutritional and metabolic processes. Substances include those described in 21CFR170.3(o), for example anti-caking agents, binders, mixing aids, preservatives, stabilizers, and substances added for aroma or flavor.

2.5. Common categories of substances

Additional analysis was conducted on five common categories of substances: Fats and Oils, Enzymes, Probiotics, Sweeteners, and Carotenoids. The information provided within the GRAS Notification was used to determine whether a substance fit into one of these five common categories.

2.6. Analysis of GRAS warning letters

All information pertaining to warning letters regarding GRAS substances was extracted from the FDA Warning Letters database (United States Food and Drug Administration, 2017b) on 26 March 2017. Searching for the term: generally recognized as safe returned 366 warning letters, while only 39 were returned when searching for the term: generally regarded as safe, and 59 were returned for the search term: GRAS. The analysis described here focuses on these 59 warning letters identified with the search term: GRAS.

3. Results

3.1. Duration of time from filing to closing

The increasing rate of GRAS Notifications submitted to the FDA is demonstrated by the shortened length of time between the filing dates for the first and last GRAS Notification in each set of 100 GRAS Notifications (Table 1). For example, the first 100 GRAS Notifications accumulated in just over 4 years (1998–2002, 1493 days), while GRN #501 to #600 accumulated in just over one and one-half years (2014–2015, 591 days), or about one-third the amount of time.

More than 63% (378) of the first 600 GRAS Notifications were resolved within 180 days of filing, 37% (221) took longer than 180 days, and 13% (77) took more than 270 days to resolve (Table 2). The average duration of time in which the GRAS Notifications were resolved remained consistent over the course of the program, averaging 201 days per GRAS Notification. Similarly, the length of time to resolution was similar between GRAS Notifications, regardless of outcome: "No Questions" averaged 204 days, "Withdrawn" averaged 189 days, and "No Basis" averaged 175 days.

The FDA consistently provided the majority of GRAS Notifications with a "No Questions" response during the Interim Pilot Program (ranging from 72 to 84 per group of 100 GRAS Notifications). The number of "Withdrawn" GRAS Notifications represented a minority of the outcomes during the Interim Pilot Program, and the number remained consistent as well (ranging from 14 to 18 per group of 100 GRAS Notifications). However, the number of "No Basis" outcomes per 100 GRAS Notifications reduced dramatically after the first group of GRAS Notifications, which included 15 "No Basis" outcomes. The remaining five groups of 100 GRAS Notifications had either 0 or 1 "No Basis" outcomes, with only 2 "No Basis" outcomes occurring in the most recent 500 GRAS Notifications.

Table 1
Date ranges for notifications in the Interim Pilot Program.

	Filing Dates	Total number of Days from First to Last Filing
0–100	10 Feb 1998 – 14 Mar 2002	1493
101–200	19 Mar 2002 – 1 Jun 2006	1535
201–300	5 Jun 2006 – 21 Jul 2009	1142
301–400	23 Jul 2009 – 25 Aug 2011	763
401–500	28 Sep 2011 – 18 Feb 2014	874
501–600	18 Feb 2014 – 2 Oct 2015	591

3.2. Number of US and international GRAS notifications

The number of GRAS Notifications received annually during the Interim Pilot Program from US-based companies ranged from 9 in 1998 to 33 in 2010 (Fig. 2), with an average of 19 per year. During this same period, GRAS Notifications from companies located outside of the US ranged from 2 in 2000 to 44 in 2014, with an average of 15 per year. Over the last five years (from 2011 to 2015), the FDA reviewed more non-US notifications (average of 28) than US notifications (average of 21) annually, unlike any of the 13 prior years (from 1998 to 2010).

3.3. GRAS notification outcomes

A majority (81%, or 485 notifications) of the outcomes from the first 600 GRAS Notifications in the Interim Pilot Program was a "No Questions" response from the FDA, while a minority (17%, or 99 notifications) were "Withdrawn" at the request of the notifier (Table 3). Few GRAS Notifications (3%, or 17 notifications) received a "No Basis" decision from the FDA, including only one GRAS Notification since 2003 (GRN #328, closed on 20 May 2011).

Over the course of the Interim Pilot Program, 400 GRAS Notifications (exactly two-thirds of those reviewed) included the conclusions from a GRAS Expert Panel. The percentage of GRAS Notifications including a GRAS Expert Panel was greatest for "Withdrawn" GRAS Notifications (73%, or 72 out of 99 notifications), followed by GRAS Notifications receiving a "No Questions" response (66%, or 320 out of 485 notifications), and was least for GRAS Notifications receiving a "No Basis" response from the FDA (41%, or 7 out of 17 notifications). In addition, GRAS Notifications for substances providing a nutritive function (79%, 220 out of 279 notifications) or technical effect (66%, 147 out of 222 notifications) were at least twice as likely to include the conclusions from a GRAS Expert Panel as GRAS Notifications for processing aids (33%, 33 out of 100 notifications).

3.4. GRAS notifications for common categories of substances

Five common categories of substances (Fats and Oils, Enzymes, Probiotics, Sweeteners, and Carotenoids) make up nearly one-third (34%, or 205 notifications) of the first 600 GRAS Notifications. In these five common categories of substances, GRAS Notifications receiving a "No Questions" response ranged from 83% for fats and oils to 100% for sweeteners (Table 4).

3.4.1. Fats and oils

GRAS Notifications for substances in the category of fats and oils included a number of substances with a nutritive purpose, providing either a blend of fatty acids or specific fatty acids for a variety of foods. The average time from filing to closure for these GRAS Notifications was 218 days, with 27 (66%) resolving within 180 days of filing, and 4 failing to resolve within 360 days of the filing date (GRN #41 DHASCO and ARASCO, GRN #94 DHA-rich tuna oil, GRN #384 algal oil, GRN #486 oil from *Buglossoides arvensis*). As with most substances with a nutritive purpose, a high percentage of GRAS Notifications for fats and oils (86%) included the conclusions of a GRAS Expert Panel.

3.4.2. Enzymes

Enzymes are the most common category of substances that are the subject of GRAS Notifications, representing 12% (70 out of 600 notifications) of the first 600 GRAS Notifications. A majority (69%, or 48 out of 70 notifications) of the GRAS Notifications for enzymes were closed within 180 days, while only 1 of the 70 notifications for enzymes failed to close within a year (GRN #402 peroxidase).

Table 2
Duration of notification resolution.

GRN Number	Notification duration		Average notification duration in days (number of notifications with the outcome)			
	>180 days	>270 days	Overall	No Questions	Withdrawn	No basis
0–100	27	13	176	175 (72)	197 (14)	159 (15)
101–200	23	6	228	199 (82)	358 (17)	175 (1)
201–300	48	14	220	235 (82)	154 (18)	NA (0)
301–400	30	16	190	205 (82)	106 (17)	434 (1)
401–500	54	22	219	237 (82)	139 (18)	NA (0)
501–600	39	6	174	174 (85)	173 (15)	NA (0)
Total	221	77	201	204 (485)	189 (99)	175 (17)

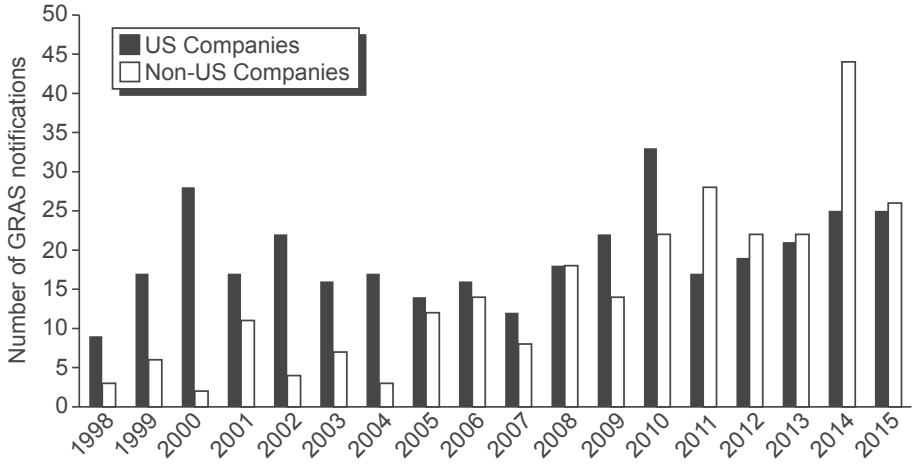

Fig. 2. GRAS notifications from US and Non-US Companies, 1998 to 2015.

Table 3
Notifications with outcomes by functional purpose.

	No Questions		Withdrawn		No Basis		Total	
	Number[a]	GRAS Expert Panel[b]	Number[a]	GRAS Expert Panel[b]	Number[a]	GRAS Expert Panel[b]	Number[a]	GRAS Expert Panel[b]
Nutritive	211 (76%)	169 (80%)	61(22%)	49 (80%)	7 (3%)	2 (29%)	279 (46%)	220 (79%)
Processing aids	93 (93%)	29 (31%)	4 (4%)	2 (50%)	3 (3%)	2 (67%)	100 (17%)	33 (33%)
Technical effect	181 (82%)	123 (68%)	34 (15%)	21 (62%)	7 (3%)	3 (43%)	222 (37%)	147 (66%)
Total	485 (81%)	320 (66%)	99 (17%)	72 (73%)	17 (3%)	7 (41%)	601 (100%)	400 (67%)

[a] The number/percentage of GRAS Notifications refers to the total number/percentage of GRAS Notifications for each functional purpose (nutritive, processing aid, technical effect) with the outcome.
[b] The number/percentage of GRAS Notifications with an Expert Panel refers to the number of GRAS Notifications for each functional purpose (nutritive, processing aid, technical effect) including a GRAS Expert Panel with the GRAS Notification outcome (No Questions, Withdrawn, No Basis).

Table 4
GRAS Notifications for common categories of substances.

	Fats and Oils	Enzymes	Probiotics	Sweeteners	Carotenoids
Substance class	Nutritive	Processing aid	Nutritive	Technical effect	Nutritive
Total notifications	41	70	21	50	23
No Questions	83% (34)	97% (68)	95% (20)	100% (50)	87% (20)
Withdrawn	12% (5)	3% (2)	5% (1)	0	13% (3)
No Basis	5% (2)	0	0	0	0
Expert Panel	78% (32)	33% (23)	100% (21)	96% (48)	91% (21)
Average EDI	465 mg/kg	4.43 mg/kg	1.8×10^{-11} cfu/day	High intensity: 4.28 mg/kg Other: 684 mg/kg	0.330 mg/kg
Duration of review: Average (range, days)	218 (42–1567)	168 (45–422)	243 (84–643)	189 (115–406)	166 (48–226)

Nearly all (97%, 67 out of 70 notifications) of the GRAS Notifications for enzymes that have resolved received a “No Questions” response from the FDA even though only 33% (23 out of 70 notifications) had a GRAS Expert Panel.

3.4.3. Probiotics

Probiotic substances include only microorganisms that provide a probiotic function (live microorganism) in food. All GRAS Notifications for probiotics included the conclusions from a GRAS Expert Panel, and all but one (GRN #409 – *Lactobacillus reuteri* strain NCIMB 30242, withdrawn) received a "No Questions" response from the FDA. This group of 21 GRAS Notifications had the longest (243 days) average time for review of these five common categories of substances, with only 43% (9 notifications) of the GRAS Notifications closing in less than 180 days. While only one probiotic GRAS Notification (GRN #49 *Bifidobacterium lactis* strain Bb12 and *Streptococcus thermophilus* strain Th4) had a review lasting longer than one year, 52% (11 notifications) of the notifications closed between 200 and 350 days after the filing date.

3.4.4. Sweeteners

The first 600 GRAS Notifications included 50 notifications with a technical effect as a sweetener. The majority of these 50 GRAS Notifications (70%, or 35 notifications) were for Rebaudiosides, and 26 of these were specifically for Rebaudioside A. All GRAS Notifications for sweeteners received a "No Questions" response from FDA, and all but 2 of these GRAS Notifications (GRN #184 isomaltulose, GRN #208 erythritol) included a GRAS Expert Panel. The FDA provided their "No Questions" response in less than 180 days for 36 (72%) of these GRAS Notifications, and only one notification (GRN #337 enzyme-modified steviol glycosides preparation) took longer than a year to resolve. The average EDI for the substances in this category was divided between high intensity sweeteners (e.g. *Stevia* and *Stevia* extracts, which had low average EDIs) and other sweeteners (erythritol, D-psicose, sucromalt, isomaltulose, D-tagatose, and trehalose, which had higher average EDIs).

3.4.5. Carotenoids

Carotenoids that were the subject of GRAS Notifications were manufactured using a variety of methods including chemical synthesis, extraction from plant material, and production using microorganisms. While the FDA had provided a "No Questions" response for 87%, or 20 of the 23 GRAS Notifications, many responses (17 notifications) indicated "some uses may require a color additive listing." The average duration of GRAS Notification for these substances was 166 days, with 70% (16 notifications) resolving in less than 180 days, and 100% resolving within 226 days. The average EDI for this common category of substances (0.330 mg/kg body weight/day) was derived after removing GRAS Notification #210 (water soluble tomato extract). While the purpose of GRN #210 was to provide carotenoids, it is a crude extract, only a portion of which is made up of carotenoids, thus the EDI for this substance was not consistent with the EDI for the other GRAS Notifications for substances in this category.

3.5. GRAS Expert Panels

As mentioned previously, 400 of the first 600 GRAS Notifications included a conclusion from a GRAS Expert Panel. The average number of members of a GRAS Expert Panel across these 400 GRAS Notifications was 3.2, and there were some differences in the average number of Expert Panel members depending on the functional purpose of the substance: nutritive (3.4), technical effect (3.1), and processing aid (2.6). This difference is also reflected when analyzing the categories of common ingredients (Table 4), with enzymes (2.3) having the lowest average number of members per panel, and the other categories having higher average numbers of members per panel: fats and oils (3.6), carotenoids (3.1), probiotics (3.7), and sweeteners (3.3).

From these 400 GRAS Notifications, 26 individuals participated in 10 or more of the GRAS Expert Panels (Table 5), and eight of these individuals served on more than 10% of the GRAS Expert Panels. The most prolific GRAS Expert Panelist in the first 600 GRAS Notifications was Joseph Borzelleca, who served on 37%, or 148, of the first 400 GRAS Expert Panels. In addition, at least one individual from this list of prolific GRAS Expert Panelists served on 88%, or 352 of the first 400 GRAS Expert Panels, with many of the GRAS Expert Panels including multiple individuals from this list.

GRAS Notifications that included at least one of the most prolific Expert Panelists received a "No Questions" response from the FDA for 82% of the notifications (288 of 353 notifications). GRAS Notifications that included a GRAS Panel, but did not include any of the most prolific Expert Panelists, received a "No Questions" response for only 70% of the notifications (33 of 47 notifications), with a higher percentage of notifications being "Withdrawn" (Table 6). GRAS Notifications that were submitted without the conclusions from a GRAS Expert Panel received a "No Questions" response from the FDA for 82% of the notifications.

3.6. GRAS warning letters

From 2005 to 2016, CFSAN (N = 28) and 14 FDA district offices (N = 31) issued 59 warning letters referencing GRAS. Only two warning letters were issued to companies outside the US (one in Canada and one in Japan). The warning letters included diverse subjects, most typically for misbranding and/or adulteration (Table 7). Sometimes, these warning letters were issued in groups to multiple companies for the same type of violation (e.g., methylsynephrine, Beta-methylphenethylamine (BMPEA) and picamilon food components considered unsafe food additives or misbranded dietary supplements).

3.6.1. Warning letter case study: caffeine and alcohol

Four warning letters were issued on the same day (17 November 2010) to four separate food manufacturers because the FDA determined that adding caffeine to alcoholic beverages was unsafe. One of the four manufacturers had submitted GRN # 347 with evidence that the combination of caffeine and alcohol was safe; however, this GRAS Notification was withdrawn after the company received the warning letter from the FDA. The language in the four warning letters was quite similar: " … the GRAS status of caffeine when directly added to an alcoholic beverage … [must have] consensus among qualified experts that the substance is safe under its conditions of use, based on publicly available data and information."

These warning letters state "*… a number of qualified experts have concerns about the safety of caffeinated alcoholic beverages. Moreover, the agency is not aware of data or other information to establish the safety of the relevant conditions of use for your products. Therefore, the*

Table 5
Most prolific GRAS Expert Panelists.

Expert	Number of panels	Expert	Number of panels
Joseph Borzelleca	148	Robert Martin	18
John Thomas	60	William Waddell	18
Michael Pariza	58	Susan Cho	17
Robert Nicolosi	48	Eric Johnson	17
Madhusudan Soni	48	Robert Kapp	14
Richard Kraska	45	Roger Clemens	13
Robert McQuate	45	George Fahey	13
Walter Glinsmann	41	Claire Kruger	12
Stephen Taylor	33	John Doull	11
Ian Munro	27	Wallace Hayes	11
Stanley Tarka	25	Douglas Archer	10
W. Gary Flamm	24	Robert Kleinman	10
Gary Williams	24	Glenn Sipes	10

Table 6
GRAS outcome based on panel.

Notification Outcome	No Expert Panel[a]	Expert Panel with no Expert Panelist listed above[a]	Expert Panel with at least one Expert Panelist listed above[a]
No Questions	82% (163)	70% (33)	82% (288)
Withdrawn	14% (27)	28% (13)	17% (59)
No Basis	5% (10)	2% (1)	2% (6)
Total	200	47	353

[a] The percentage (number) of GRAS Notifications refers to the total percentage/number of GRAS Notifications with each outcome (No Questions, Withdrawn, No Basis) depending on whether a GRAS Expert Panel was included, and whether or not that Expert Panel included at least one of the most prolific GRAS Expert Panelists.

Table 7
Warning letters referencing GRAS/GRASE.

Subject	Count
Methylsynephrine/Labeling/Dietary Supplements/False & Misleading/Misbranded	7
cGMP/Misbranded/Adulterated/Dietary Supplement/Finished Pharmaceuticals	6
Unapproved Food Additive/Nutrient and Health Claims/Adulterated/Misbranded	6
BMPEA/Labeling/Dietary Supplements/False & Misleading/Misbranded	5
Picamilon/Labeling/Dietary Supplements/Misbranded	5
Labeling/Adulterated/Dietary Supplements/False & Misleading Claims/New Drug/Food Additive/Misbranded	4
Dietary Supplement/Adulterated//Promotional Claims False & Misleading/Misbranded	4
Illegal Food Additive/Adulteration	4
Adulterated Food/Misbranded/Labeling	3
Unapproved New Drug/Adulterated/Misbranded	3
Food Additive/Adulterated/Misbranded	2
Food Labeling Regulation/Food Additive Misbranded	2
Seafood HACCP/CGMP for Foods/Adulterated/Insanitary Conditions	2
Illegal Drug Residue Animal Tissue/Adulterated	1
Interstate Commerce/Food/Adulterated	1
Medical Foods and New Drug Labeling/Internet Claims/Misbranded	1
New Animal Drug/Adulterated/Misbranded	1
New Drug/Misbranded	1
Premarket Approval/Misbranded/Adulterated	1
TOTAL	**59**

criteria for GRAS status have not been met for the caffeine in your beverages … Reports in the scientific literature have raised concerns regarding the formulation and packaging of pre-mixed products containing added caffeine and alcohol. For example, these products, presented as fruity soft drinks in colorful single-serving packages, seemingly target the young adult user … [and] appears to be specifically directed to young adults (Bonnie and O'Connell, 2004). FDA is concerned that the young adults to whom these pre-mixed, added caffeine and alcohol products are marketed are especially vulnerable to the adverse behavioral effects associated with consuming caffeine added to alcohol, a concern reflected in the publicly available literature (O'Brien et al., *2008; Simon and Mosher, 2007)*"

The FDA emphasized GRAS determination is "not an inherent property of a substance" and the intended use of the substance is critical to the determination of whether a substance is GRAS. The FDA also clearly and rather consistently defined the terminology for food additive, GRAS eligibility, scientific procedures, common use in food, and safe/safety in these warning letters.

3.6.2. Warning letter case study: stevia

Another four of the 59 warning letters were issued about stevia, identified as an unsafe food additive in four specific situations. Two warning letters were issued in 2006 and 2007, prior to the first GRAS Notification for these substances (GRN #252, filed on 13 May 2008). Both of these warning letters indicated conventional food products including stevia were adulterated because stevia is not an approved food additive for the uses identified, stevia is not a dietary supplement, and these substances did not have GRAS status because published studies *"raised safety concerns"* about the use of stevia, *"including concerns about control of blood sugar, and effects on the reproductive, cardiovascular and renal systems."* The second warning letter also stated *" … FDA has received inquiries and petitions for the use of stevia or stevia extracts in food, data and information necessary to support the safe use have been lacking."*

Two additional warning letters were issued in 2012 and 2015 about the form of stevia used in foods. In 2012, one company received an FDA warning letter stating *" … three of your products … are labeled to contain stevia. Whole-leaf and crude stevia extracts are not approved for food use as a sweetener. Certain highly purified steviol glycosides obtained from stevia leaves have been the subject of generally recognized as safe (GRAS) notices. FDA has not objected to the use as sweeteners of these highly refined substances, which are generally referred to as Rebaudioside A".* Similarly, in 2015, another company received an FDA warning letter for using stevia leaf in tea. This warning letter cited the lack of a food additive regulation, prior sanction or GRAS status for the use of Stevia leaf in conventional foods and stated *"Stevia leaf is not approved for use in any food, including teas …"* and the FDA concluded the food products containing stevia leaf were adulterated.

Since December 2008, certain highly purified steviol glycosides obtained from stevia leaves have been the subject of at least 46 GRAS Notifications. In general, FDA has not objected to the use of these highly-refined substances, which are generally referred to as Rebaudiosides and used as sweeteners. All of these stevia-related GRAS Notifications have received a "No Questions" response from the FDA, except two pending resolution (GRN # 607 for "Glucosylated steviol glycosides, GRN # 667 for Rebaudioside M).

4. Discussion

Numerous papers have reviewed the history of the GRAS process in the United States (Burdock, 2000, 2015; Burdock and

Carabin, 2004; Burdock et al., 2006; Day, 1976; McColl and Janus, 2016; Neltner et al., 2013; Siu et al., 1977). In addition, many specific GRAS substances have been reviewed in the literature, including: sodium (Cobb et al., 2012); inulin and oligofructose (Coussement, 1999); partially hydrogenated oils (Covington & Burling, 2015); long-chain omega-3 fatty acids (Fenton et al., 2013); mono-sodium glutamate (Geha et al., 2000); multilayer films (Hsu et al., 2014); guayusa concentrate (Kapp et al., 2016); probiotics (Mattia and Merker, 2008); nonnutritive sweeteners (Roberts and Wright, 2012); caffeine (Rosenfeld et al., 2014); colicins (Schulz et al., 2015); diacylglycerol (Takase, 2007); and cinnamaldehyde (Upadhyaya et al., 2015).

As opposed to focusing on the history of the GRAS process, the mechanism underlying how a substance is determined to be GRAS, or investigating specific substances that have undergone evaluation in the GRAS process, this article conducts a high-level assessment of the first 600 GRAS Notifications submitted to the FDA during the Interim Pilot Program. As reported by others previously (Roberts and Haighton, 2016), most of the first 600 GRAS Notifications (81%) have received a "No Questions" response from the FDA, 3% of the submissions received a "No Basis" response from the FDA, and 17% were "Withdrawn" (Table 3). Although the number of submissions over time has increased dramatically (Table 1), the duration of the GRAS Notifications have stayed relatively constant (Table 2), averaging between 176 and 228 days for each group of 100 Notifications. It is impressive that the FDA has been able to maintain a consistent average, despite this large increase in volume of GRAS Notifications over the course of the Interim Pilot Program.

The proposed GRAS rule published in 1997 (United States Food and Drug Administration, 1997), indicated the FDA would respond to the notifier in writing within 90 days. Likely based on the learnings from the Interim Pilot Program, the GRAS final rule (United States Food and Drug Administration, 2016b), indicates the FDA will respond to a notification within 180 days, with a potential for a 90 day extension to be added for further consideration (meaning up to 270 days total for review). This timing appears to be realistic, as during the Interim Pilot Program only 37% (221 notifications) of the first 600 GRAS Notifications took longer than 180 days to resolve, and only 13% (77 notifications) took more than 270 days to resolve.

During the Interim Pilot Program, a small number of GRAS Notifications took an exceptionally long time to resolve. Within each set of 100 GRAS Notifications, the maximum times to closures were: 1567 days (GRN #94), 2155 days (GRN #194), 1357 days (GRN #251), 476 days (GRN #336), 776 days (GRN #478), and 418 days (GRN #540). Less than 5% (26 notifications) of the first 600 GRAS Notifications took longer than one year to resolve, only 1.8% (11 notifications) took longer than 2 years. The number of GRAS Notifications taking an exceptionally long time to resolve appears to be decreasing, as only one notifications in the most recent 100 GRAS Notifications took longer than one year to resolve (GRN #540).

The duration of a GRAS Notification was similar between substances with a nutritive (210 days) and technical effect (207 days), but was shorter for processing aids (164 days). Interestingly, for substances with the same general functional effect (nutritive, processing aid, or technical effect), analysis (Table 4) revealed that the duration of the GRAS Notification could be correlated to the more specific common categories. For example, the average review length for probiotics was more than two months longer than the average review time than that for carotenoids, suggesting that added complexity for probiotic substances (such as questions regarding mechanism of action or specifications for the microbial speciation) may result in a longer review times for the FDA.

Specific factors impacting resolution of a notification within 180 days were not readily apparent based on the criteria used in this evaluation, however general trends were observed. For example, there were a higher percentage of notifications that resolved in greater than 180 days received than those that resolved in 180 or fewer days for: notifications that received a No Questions response from the FDA (87% vs. 77%, respectively), included the conclusions of a GRAS Expert Panel (73% vs. 63%, respectively), or were for substances with a nutritive purpose (53% vs. 42%, respectively). Increased time of resolution for notifications that receive a No Questions response from the FDA could in part be explained by the need for additional time to successfully address questions that were raised during the review, whereas if significant data gaps arise early in the review that are not otherwise easily overcome this could lead to faster (negative) resolution of notifications. Alternatively, notifications that are potentially more complicated (as evidenced by those that a GRAS Expert Panel was commenced or based on the function of the substance, e.g. nutritive) are more likely to resolve in more than 180 days. However, none of the parameters evaluated in this paper gave a clear advantage in terms of ensuring that notifications resolved in less than 180 days, rather the most reasonable conclusion is that this is instead under the most control by the specific circumstances of each individual substance. As would be expected, notifications that included a robust and careful assessment of the chemical composition of an ingredient and its associated safety literature would be more well received, as well as those notifications that had clear standards previously established in performing safety assessments (e.g. enzymes, processing aids).

4.1. International impact to GRAS

During the course of the Interim Pilot Program, the GRAS Notification program shifted from being dominated by domestic companies to a program with a significant contribution from non-US companies (Fig. 2). The increase in the number of annual GRAS Notifications was strongly influenced by the large increase in the number of GRAS Notifications from non-US companies. For example, during the first 9 years of the Interim Pilot Program (1998–2006) an average of 7 notifications per year were from non-US companies per year, while in the last 9 years of the Program (2007–2015) the average more than doubled to 23 notifications per year.

In the preamble to the GRAS final rule, the FDA acknowledges the volume of GRAS Notifications from non-US companies and suggests this international involvement demonstrates the global value of the FDA GRAS Notification process. This global value for the GRAS Notification process could manifest in several ways and these highlight the increasingly global nature of the food supply. For example, non-US companies could be using the GRAS Notification process to enable business opportunities within the US. Furthermore, because of the respect many international food regulators have for the US FDA, non-US companies could be using the GRAS Notification process to gain an important regulatory reference for open, global markets using the US FDA regulatory process as a basis for their own food systems.

4.2. GRAS Expert Panels

Of particular note in this report is the finding of 26 individuals who have served on ten or more of GRAS Expert Panels with at least one of these prolific Expert Panelists being included in 88% (352 notifications) of first 400 GRAS Expert Panels. This suggests a perceived value in having experts with extensive GRAS Expert Panel experience in addition to relevant scientific training on the Expert Panel. Additionally, the percentage of notifications that included a prolific GRAS Expert that received a No Questions response from the FDA (82%, or 288 of 352 notifications) was higher

than those notifications that had a GRAS Expert Panel but did not include a prolific GRAS Expert (69%, or 33 of 48 notifications). Caution should be used when interpreting these results due to several factors, importantly the relatively small sample size (48 versus 352 notifications). Also of interest is the finding that GRAS Notifications for substances serving a nutritive (78%) or technical effect (66%) were more likely to include the conclusions of an Expert Panel than GRAS Notifications for substances serving as a processing aids (33%).

Ultimately, the decision about whether a GRAS Expert Panel is helpful to support a GRAS determination will be based on a case-by-case examination of the available information. This evaluation shows an Expert Panel was included in two-thirds (400), but not included in one third (200) of the first 600 GRAS Notifications evaluated by the FDA in the Interim Pilot Program.

Interestingly, of the 70 enzyme GRAS Notifications during the Interim Pilot Program, 47 (67%) did not include a GRAS Expert Panel, and 97% (46 out of 47 notifications) of these GRAS Notifications received a "No Questions" response from the FDA. The FDA has published specific guidance (United States Food and Drug Administration, 2010) specifying much of the information that should be included as part of a GRAS Notification for enzyme preparations. However, this guidance does not suggest that the conclusions of a GRAS Expert Panel are necessary, only indicating that "This determination can be made by qualified experts outside of government." In the context of the GRAS Final Rule, 21CFR170.250(b), it will be interesting to determine whether the requirement to "provide a basis for your conclusion that the notified substance is generally recognized, among qualified experts, to be safe under the conditions of its intended use" could be fulfilled through means other than the inclusion of a conclusion from a GRAS Expert Panel, such as through the review of the experts within the FDA, or through reference to other previously approved enzyme preparations.

4.3. Expectations for self-affirmed GRAS conclusions

The analysis presented here focused only on GRAS determinations submitted to the FDA as part of the Interim Pilot Program. In addition to these publically accessible GRAS Notifications, individuals may self-affirm the GRAS status of a substance and chose not to conduct the voluntary notification to the FDA. In the final rule, the FDA confirmed the Agency lacks "express[ed] statutory authority to require companies to submit GRAS notices" and indicated the self-affirmed GRAS conclusions (also known as an independent conclusion of GRAS) are appropriate. However, the Agency re-iterated that the principles in the GRAS final rule are applicable to both the GRAS determinations submitted to the FDA (GRAS Notifications) as well as the self-affirmed GRAS determinations. For example, the FDA advises: "In considering whether GRAS criteria are satisfied because the available data and information demonstrate that the use of a substance is safe and the safety is generally recognized, we do not distinguish between a conclusion of GRAS status submitted to us as a GRAS notice and an independent conclusion of GRAS status that remains with the proponent." In addition, the FDA announced its intentions to publish guidance on "the importance of maintaining the data and information that support an independent conclusion of GRAS status", including a "Frequently asked questions about GRAS" guidance published in October 2016 (United States Food and Drug Administration, 2016a).

One of the best known examples of independent GRAS conclusions are those conducted by the Flavor and Extract Manufacturers Association (FEMA). The history (Adams et al., 1996; Hallagan and Hall, 1995, 2009) and the FEMA process (Smith et al., 2004, 2005a, 2005b) are not discussed in detail here, but are well documented in the published literature. The FEMA GRAS panels have reviewed more than 1700 flavor ingredients and determined most of them were GRAS (Adams et al., 1996). Similar to the most prolific Expert Panelists described above, the FEMA GRAS panels utilize experienced experts on multiple GRAS panels, and some of these experts (e.g., Samuel Cohen) have also participated in GRAS panels for substances notified to the FDA outside of the FEMA Program.

4.4. Sweeteners

The stevia warning letters provide clarity about the types of substances FDA considers under the control of food additive versus GRAS regulations, as well as the importance of the form of the substance subject to a GRAS determination. The GRAS database does not provide detail about whether manufacturers conducted independent GRAS determinations when they received their warning letters, or whether they had instead relied on other regulatory mechanisms.

Low calorie sweeteners (like aspartame and saccharine) are considered to have a high initial concern level (United States Food and Drug Administration, 2007) and have been extensively studied in the US and the EU based on their expected high exposure and toxic/carcinogenic potential. The safety concerns included carcinogenicity as well as body weight gain, glycemic control and impact on the microbiome of the GI tract. Historically, sweeteners (including acesulfame K, advantame, aspartame, neotame and sucralose) were approved as food additive petitions in a process taking "up to 10 years" to complete while the recent sweeteners (steviol glycodies and lo han guo) were entered onto the US market through the GRAS notification process (Roberts, 2016).

As noted in this paper, 70% (35) of the 50 GRAS Notifications for sweeteners were for Rebaudiosides, typically Rebaudioside A (52%, or 26 notifications) Only two of these GRAS Notifications did not include a GRAS Expert Panel (GRN #184 for isomaltulose and GRN #208 for erythritol) and all received a "No Questions" response from the FDA. Further, the FDA provided their "No Questions" response in less than 180 days for 36 (72%) of the sweetener notifications with only one notification closed over a year after the filing date (GRN #337 for enzyme-modified steviol glycosides preparation).

The proliferation of GRAS notifications for stevia-related compounds (46 notifications since 2008) provides insight into the types of GRAS determinations likely to be notified to the FDA in the future, especially since none of these GRAS Notifications resulted in a "No Basis" letter or were "Withdrawn"). For example, the FDA "No Questions" letters for the 46 stevia GRAS Notifications might continue to make the GRAS Notification a requirement for entry into the market for a new stevia-derived product or at least encourage a company to self-affirm their stevia ingredients as GRAS without notification.

4.5. Warning letters

The warning letters presented here highlight similar concepts as described in the preamble of the GRAS final rule and these GRAS warning letters emphasize certain safety details likely to continue to be a focus for the GRAS program at the Agency. The warning letters about caffeine in alcoholic beverages show how a GRAS determination is not for a substance, per se, but rather for a particular intended use of a substance. These warning letters also emphasize concern about sensitive subpopulations (young adult users) and provide a thorough rationale to explain why publicly-available literature which expresses a concern about a substance is considered during the GRAS status determination for a specific

intended use. In addition, the stevia warning letter examples should lead food manufacturers to be cautious about the use of certain unprocessed botanical food substances (like leaves, stems or other plant parts), even if extracts or compounds from these substances have already been determined to be GRAS with the FDA. For complex food components from plants, like stevia, which experience seasonal, climatic, or other variability, these warning letters also emphasize the importance of having well defined specifications.

The FDA uses warning letters as a voluntary form of enforcement and to encourage appropriate interpretation of the scientific literature supporting the safety of an ingredient with reference to the principles of the GRAS process, i.e. "general recognition" and "scientific consensus among qualified experts". Firms who receive warning letters are encouraged to correct the alleged violations or in some cases to withdraw the potentially unsafe products from the market in order to avoid additional enforcement actions by the FDA. For GRAS substances, food-related companies should be aware the FDA does issue warning letters when GRAS requirements are not met. In particular, the FDA has repeatedly used the warning letter enforcement process to remove particular ingredients or ingredient combinations from the US market (e.g., ephedra, stevia plant components and whole leaf extracts, mixtures of caffeine and alcohol, melatonin, dimethylamylamine, ginko, BMPEA, picamilon, methylsynephrine and others).

5. Conclusions

Since the initiation of the Interim Pilot Program in 1997, the GRAS Notification process has served as an important mechanism for the review of new substances being introduced into the food supply in the United States. Analysis of the notifications submitted during the Pilot Program enforces the principles that the Agency has emphasized during the modernization of the process, including the publication of the GRAS Final Rule in August of 2016. In addition, the FDA continues to use warning letters to encourage voluntary compliance with the GRAS Final Rule. Following these principles and FDA inspectional practices, the GRAS Notification process will continue to ensure the safety of food substances marketed in the United States, and the GRAS Notification process will continue to serve as a key reference for global food safety programs.

Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.fct.2017.03.064.

Transparency document

Transparency document related to this article can be found online at http://dx.doi.org/10.1016/j.fct.2017.03.064.

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