Spoke

Solving Solubility with Science

Generally Recognized as Safe (GRAS)

In this Brief we share general background information on GRAS designations

Technical Brief

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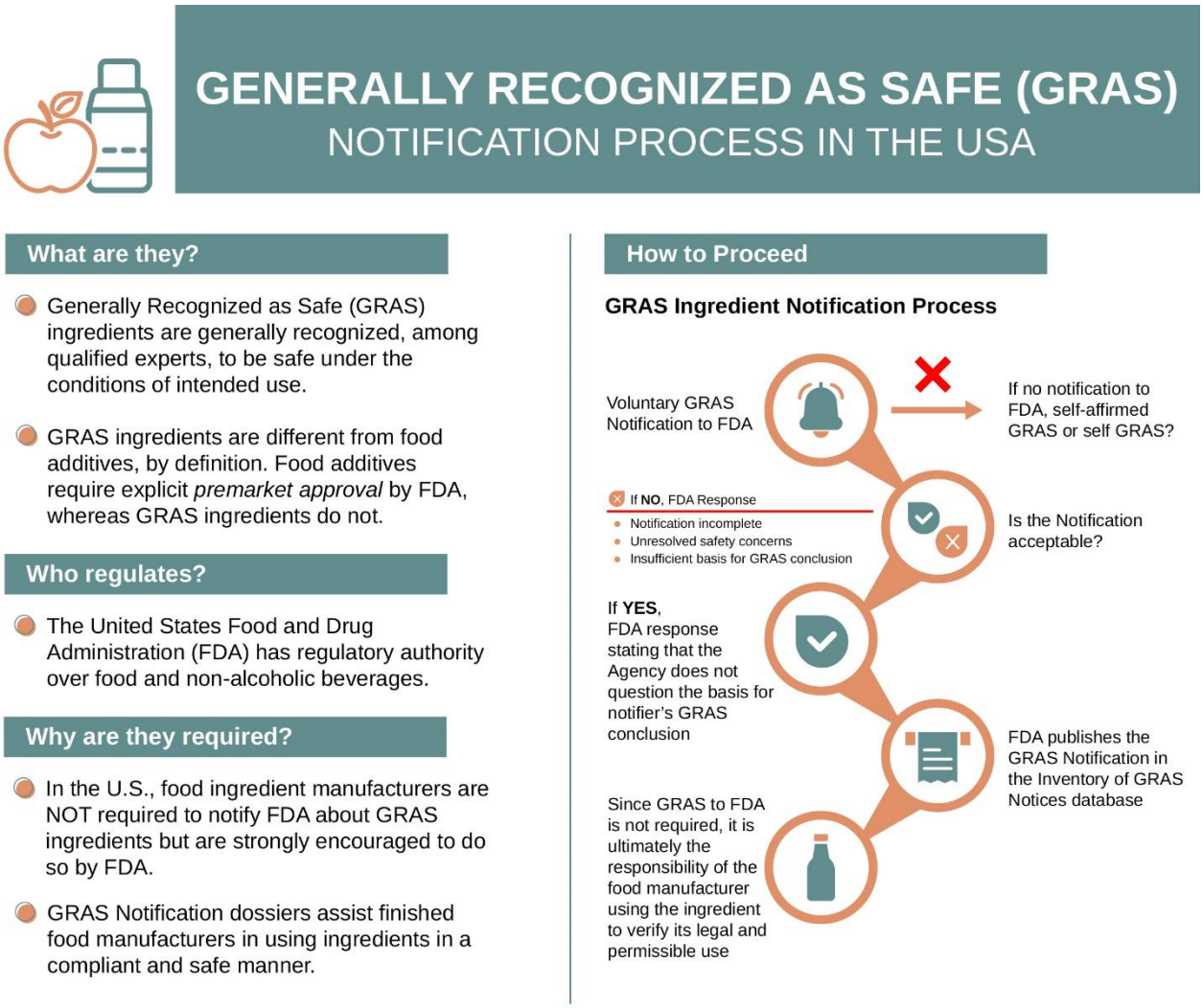
Introduction to GRAS (Generally Recognized as Safe)

The Generally Recognized As Safe (GRAS) for food-use pathway was established by the 1958 Food Additives Amendment to the Federal Food, Drug, and Cosmetic Act (FD&C Act). Under the 1958 Food Additives Amendment, 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" (the GRAS provision) or otherwise excepted from the definition of a food additive, e.g. color additive. The passage of the Dietary Supplement Health and Education Act of 1994 further amended the FD&C Act to permit new dietary ingredients (NDI) for use in dietary supplements, a subcategory of food. These two pieces of legislation helped define the three pathways by which new ingredients can be introduced into food and dietary supplements in the U.S.: 1) GRAS, 2) Food Additive Petition and 3) New Dietary Ingredient Notifications.

Fig. 1



This Technical Brief describes how the GRAS pathway works and how GRAS ingredients are different from related pathways. This short article is not meant to provide an in-depth review of the GRAS process, but two key points are nonetheless worth emphasizing: 1. specific use, and 2. specific user.

1. Specific use

A substance is deemed GRAS for a specific use and under specific conditions

Specific Use
GRAS status for one function does not equate to GRAS status for any other function.

Example: Substance A is GRAS for the technical function of emulsification. Unless Substance A is also GRAS for use as an anti-caking agent, then it cannot be used in food as an anti-caking agent merely because it is GRAS for use as an emulsifier.

Specific Conditions
An article may be required to meet certain ingredient specifications for purity and/or may be subject to concentration limits to achieve the GRAS function.

Example: Substance A is required to have purity greater than 90% A and contain less than 1% of Substance B, a known impurity, to be GRAS compliant. In addition, Substance A must be used below a certain concentration limit (e.g. 500 ppm) and is only permitted for certain types of products (e.g. non-alcoholic beverages).

2. Specific user

A GRAS notification is specific to the company filing the notification

Specific to Company
When an article and use is GRAS, technically *only* the firm that submitted the GRAS notification is conferred GRAS status. Having said that, while the FDA possesses the authority to enforce the firm-specific nature of GRAS, it generally chooses not to do so.

Example: Company 1 receives a "no questions asked" response from FDA for a GRAS Notification for Substance A. If Company 2 also wishes to manufacture Substance A, Company 2 must separately pursue GRAS eligibility.

Why is GRAS important?

There are a number of practical reasons why firms that produce ingredients for use in food or dietary supplement products would seek to pursue the GRAS pathway:

Legal and Non-adulterated Products

Almost all firms that produce food products for the United States market, including beverage manufacturers, and most dietary supplement manufacturers, will not use ingredients that do not have a history of use in food or that cannot be legally-marketed. Doing otherwise creates an adulterated product that is subject to market removal and potential criminal charges.

For ingredients that do not have a history of use as articles used for food, the only way for an ingredient to be legally-marketed is:

- Upon successful submission of a GRAS notification to FDA or the completion of a self-affirmed GRAS assessment (see Fig. 1)
- Upon successful submission of a new dietary ingredient notification (NDIN) to FDA

-OR-

- Upon regulatory change resulting from a Food Additive Petition (FAP)

Establishing safety

An integral part of any GRAS dossier is the basic demonstration of acceptable risk (*cf.* safety) for the named substance and any impurities that might be present. This includes any byproducts that may be introduced by the manufacturing process. Whether one is interested in pursuing a GRAS Notification for submission to FDA or for a self-affirmed GRAS conclusion, the process involves an evaluation of safety for the conditions of use (e.g. serving size, no-observed adverse event level, etc.).

Beyond the ethical and regulatory necessity of understanding the hazards of a product meant for human consumption, pursuing GRAS helps protect a firm from product liability in the event that harm ensues. But more importantly, GRAS helps to prevent the potential hazard in the first place. That is always good for business.

Avoiding drug preemption

Section 201(ff)(3)(B) of the FD&C Act disqualifies an ingredient from use in food or dietary supplement products if the ingredient is 1) an active ingredient in an approved drug or 2) if substantial clinical investigation of the substance as a drug has been conducted AND made public. In other words, if an article is a drug, it cannot be a food or dietary supplement. This creates a race-to-market situation for articles used in food versus articles used in drugs.

Importantly, it is FDA's position that "legal" marketing entails more than simple inclusion of the substance in marketed products—the substance must have been the subject of GRAS, food-additive, or new dietary ingredient notification (NDIN) pathways, if required, to be *legally* marketed

How is GRAS Accomplished?

There are two means by which GRAS-status can be achieved. The first involves officially, but voluntarily, notifying FDA of the GRAS dossier via a GRAS Notification. The second, "self-affirmed GRAS" (Self-GRAS), does not involve any submission to FDA.

Both a GRAS Notification and self-GRAS involve the creation of a GRAS dossier that demonstrates the acceptable (*cf.* safe) conditions for use of the article in food. As depicted in Figure 1, the only difference between the two is what happens after the completion of the GRAS dossier.

Determining whether to pursue a GRAS Notification to FDA or Self-GRAS can often turn on a number of perceived advantages/disadvantages of Self-GRAS.

Advantages:

- Convene own panel of independent experts to decide if data warrants GRAS
- Maintain confidentiality of GRAS dossier

Disadvantages:

- Self-GRAS does not allow FDA to opine on the sufficiency/adequacy of a GRAS dossier
- Perceived as lacking a "seal-of-approval" from FDA

Conclusion

In the United States, any manufacturer of finished food products is ultimately responsible for producing safe and legal products. One critical step in doing so is to deal only with suppliers that thoroughly understand and comply with Federal requirements such as GRAS and GMPs.

Spoke Sciences builds regulatory strategy and compliance into our solutions. We do not simply solve the solubility problem for your favorite ingredients, we also incorporate regulatory intelligence to up-level your compliance. Please contact us if you would like to learn more.