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Strategic Approaches for Establishing a Suitable U.S. Regulatory Status for Food Ingredients and Dietary Supplements

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Whether exploring U.S. market entry for a novel microbial enzyme for food preparation, developing an antimicrobial used in meat or poultry processing, manufacturing a dietary supplement, or validating the regulatory status of your suppliers' ingredients used in a finished product, this advisory series breaks down what it takes to establish a suitable regulatory status for both conventional food ingredients and dietary supplements and provides insights into best practices.

This first advisory addresses foundational aspects of obtaining a suitable regulatory status for a food ingredient, including determining whether an existing regulatory clearance is applicable and understanding the FDA's petition process for food additives. Future advisories in this series will cover the generally recognized as safe (GRAS) regulatory pathway and special considerations for dietary supplements; animal feed; food ingredients used in meat, poultry, and egg products; and food-contact materials.

What Is a Food Additive?

Whether developing a novel food additive or determining the regulatory status of ingredients used in your finished food product, it is important to first understand the regulatory framework that governs the regulatory process for the manufacture, import, and sale of FDA-regulated ingredients in the U.S. The 1958 Food Additives Amendment to the Federal Food, Drug, and Cosmetic Act (FDCA) established a premarket review and approval system for food additives, effectively placing the burden of proof on industry to demonstrate the safety of a substance intentionally added to food. The FDCA defines a "food additive" as "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 …, if such substance is not generally recognized … to be safe under the conditions of its intended use."

The "food additive" definition applies when a manufacturer knows or should know that the use of any substances results in becoming a component or affecting the characteristics of any food. Importantly, the definition excludes substances that are generally recognized, "among experts qualified by scientific training and experience to evaluate its safety," to be safe under the conditions of its use. This is also known as the generally recognized as safe (GRAS) exemption. GRAS status may exist based on a level of scientific agreement about a substance's safety, or for a substance used in food before January 1, 1958, on scientific procedures or common use in food. The definition of "food additive" also enumerates other exclusions: pesticide

chemical residue in or on a raw agricultural commodity or processed food, a pesticide chemical, a color additive, prior sanctioned substances, new animal drugs, and dietary ingredients used in a dietary supplement.

Does My Product Have an Existing Regulatory Clearance?

The starting point for evaluating whether an ingredient may be used in a food product is determining whether the use of that ingredient has an applicable existing regulatory clearance. The FDA has published regulations listing food additives that are permitted in food in 21 C.F.R. Part 172 (direct food additives) and 21 C.F.R. Part 173 (indirect food additives). Direct food additives are those that are added directly to food, while indirect food additives are substances that may come into contact with food (e.g., as part of processing equipment or packaging) but are not intended to be added directly to food.

If the use is not permitted by Parts 172 and 173, you can also look to the lists of substances the FDA has already concluded or otherwise affirmed as GRAS. These lists, found in 21 C.F.R. Parts 182, 184, and 186, impose use levels and specify the functional role the ingredient must serve in the finished food to rely on the listing. Specifically, Part 182 lists some substances the agency has concluded are GRAS when used as direct or indirect food additives, and Parts 184 and 186 contain substances the agency previously "affirmed" as GRAS for use as direct and indirect food additives, respectively, through a now-retired GRAS affirmation petition process.

Note, however, that the FDA's regulations acknowledge that many substances that are GRAS are not explicitly listed in the regulations. This is particularly true for the many food ingredients of natural origin that were widely consumed before 1958. The FDA also publishes on its website an inventory of its responses to GRAS notices filed since 1998 that can also be reviewed to determine whether the FDA has issued a "no questions letter" for the use of a particular substance.

As an aside, color additives—or any dye, pigment, or other substance that imparts color—in foods must also be supported by an appropriate regulatory status. A list of FDA-approved color additives and their use indications and restrictions can be found at 21 C.F.R. Parts 73 and 74. Since there is no GRAS exemption to the definition of color additive, the use of a new color additive or a new use of a listed color additive requires FDA approval through the submission of a color additive petition to establish that the color additive is safe for the intended use.

Should no existing regulatory clearance cover a food ingredient's intended use, you can obtain an appropriate regulatory status for the ingredient through either the food additive petition (FAP) process or the GRAS pathway.

Food Additive Petition Regulatory Pathway

A manufacturer can submit to the FDA an FAP to demonstrate that a food additive is safe for its intended use. The main features of an FAP are:

- *Requirements.* Petitions must contain, among other things, the name of the proposed chemical, chemical identity, composition, conditions of use, labeling, physical effects data, technical effects (and levels) data, methods of determining quantity in food after use, and results of safety studies.
- *Review period.* The agency has the discretion to accept or deny the petition, and once accepted, the agency will publish a notice in the *Federal Register* with the name of the petitioner and a description of the proposal. While there is a statutory limit of 180 days for the FDA to act upon the FAP, this is an iterative process, with the FDA typically asking follow-up questions, extending this process well beyond the statutory limit.
- *Outcome.* Once the FDA approves an additive, the agency will issue regulations for the additive, specify the amount that may be used, and prescribe conditions necessary to ensure the approved food additive will be used safely. Use limitations may relate to levels of use, the types of foods the additive may be used in, the purpose it is used for, or the form it is marketed in.

The FAP process may be less familiar since it is used less often than a GRAS notice or reaching a self-GRAS conclusion (the latter two to be discussed in our next advisory). Ultimately, whether an entity decides to submit an FAP will depend on a number of factors, including:

(1) *The type of data available.* Under FDA regulations, an FAP requires "full reports of investigations made with respect to the safety for use of such additive, including full information as to the methods and controls used in conducting such investigations." An FAP generally relies on unpublished data or data from published studies sponsored by the entity submitting the FAP, while a GRAS conclusion must rely on publicly available data. Though the source of the data may be different for each pathway, the data standard is the same: the petitioner/entity must demonstrate the safety for the proposed use.

(2) *Customer requirements.* If successful, the FAP process culminates in FDA approval of the petitioned substance and the issuance of a regulation. The submission of a GRAS notice favorable to the agency does not result in the FDA's "approval" of the substance but rather a "no questions" letter from the agency that may be disfavored by customers in some circumstances.

(3) *Timing.* Because of the administrative rulemaking nature of the FAP process, obtaining a final rule for an FAP typically takes longer than receiving the FDA's response letter to the filing of a GRAS notice. The time it takes to come to a self-GRAS conclusion is not a function of FDA review.

Conclusion

The FDA's FAP process for food additives is one regulatory pathway regulated industry can take to establish a suitable regulatory status of ingredients used in food. Our next advisory will focus on using the GRAS pathway to get food ingredients to market and further explore the benefits and drawbacks of that approach compared with the submission of an FAP.

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