Generally Recognized as Safe (GRAS):
GMA Background and
Summary of Regulatory Requirements
HISTORICAL PERSPECTIVE

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 subject to pre-market approval by FDA unless the use of the substance is generally recognized as safe (GRAS), or otherwise exempt 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 1960s, 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 President Nixon directed FDA to reexamine the safety of the GRAS substances. In the 1970s, FDA announced that it was conducting a “comprehensive review” (SCOGS 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”).

SUMMARY OF REGULATORY REQUIREMENTS

The Generally Recognized as Safe (GRAS) regulatory construct derives from an exemption to the definition of “food additive” in § 201(s) of the Federal Food, Drug, and Cosmetic Act (FDC Act). Below is the pertinent part of that definition:

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…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.

Because the application of this definition turns on the intended use of a substance, the same substance may be regulated as a food additive with respect to one use, and may be GRAS with respect to a different use. It is therefore more accurate to speak of the specific use of a substance as being a food additive use than to speak of the substance itself as being a food additive. This important distinction is rarely observed in discussions about food additive regulation, but is fundamental to its complete understanding.

The GRAS exemption to the definition of food additive is important because food additive uses of substances must be approved by FDA prior to marketing. By virtue of being exempt from the definition of food additive, it follows that GRAS uses of substances are not subject to premarket approval. In the case of substances used prior to January 1, 1958, GRAS status can be established through experience based on common use in food, and does not require the same quantity and quality of scientific

1 FDC Act § 409.
evidence required to support food additive approval. However, a common use GRAS determination must be based solely on food use of the substance prior to that date, and must ordinarily be based on generally available information.

The use of a substance more commonly achieves GRAS status through scientific procedures. This requires the same quantity and quality of scientific evidence required to support food additive approval, and is ordinarily based on published studies that may be corroborated by unpublished studies and other data and information. Establishing GRAS status through scientific procedures thus requires that two elements be satisfied. The first is referred to as the technical element, which requires technical evidence of safety. The technical element requires information establishing that the intended use of the substance is “safe” (i.e., there must exist “reasonable certainty in the minds of competent scientists that the substance is not harmful under its intended conditions of use”). This is the same safety standard that applies to FDA’s evaluation of food additive uses of substances.

The second element that must be satisfied to establish GRAS status through scientific procedures is referred to as the common knowledge element. The common knowledge element is an important distinguishing factor between a substance that is GRAS based on scientific procedures and a safe food additive. This element requires a basis to conclude that the technical evidence of safety is both generally known and accepted. Thus, two criteria must be met: (1) the pivotal information relied on to establish the technical element must be generally available, typically in the form of publications in peer-reviewed scientific journals; and (2) there must be a basis to conclude that there is consensus (but not necessarily unanimity) among qualified experts about the safety of the intended use of the substance.

Consensus about safety can be demonstrated in a variety of ways, including by reference to peer-reviewed scientific journals, the secondary scientific literature (e.g., textbooks and scientific review articles), or the opinion or recommendation of an authoritative body (e.g., the National Academy of Sciences). Consensus can also be demonstrated by the opinion of a panel of appropriately qualified experts specially convened for the purpose of determining whether such consensus exists.

If in fact the use of a substance does not meet all of the criteria for GRAS status, then that substance would not qualify for the GRAS exemption from the definition of “food additive” with respect to that use. Marketing of that substance in the absence of a GRAS determination or a food additive approval could result in the substance being deemed an “unsafe” (meaning unapproved) food additive with respect to that use. Because GRAS status rests on both a technical element and a common knowledge element, FDA can challenge GRAS status based on alleged deficiencies with respect to either element.

---

2 21 C.F.R. § 170.30(c)(1).
3 Id. § 170.30(b).
5 21 C.F.R. § 170.3(i).
6 See supra, fn. 4.
7 Id. at 18,941.
8 Id.
9 FDC Act § 409(a).
A food additive that is “unsafe” with respect to the use in question may be deemed adulterated, as may be any food that bears or contains the food additive.\textsuperscript{10} The introduction or delivery for introduction into interstate commerce of an adulterated food is a prohibited act punishable by civil and criminal penalties.\textsuperscript{11} FDA has authority to institute judicial proceedings to enjoin commission of prohibited acts and to seize adulterated food.\textsuperscript{12}

\textsuperscript{10} Id. § 402(a)(2)(C)(i).
\textsuperscript{11} Id. § 301(a) and § 303(a).
\textsuperscript{12} Id. § 304(a)(1) and § 302.