Evaluating food-contact materials

Lester Borodinsky

ABSTRACT: The use of articles in contact with food involves both regulatory and scientific considerations when establishing the status of the components under the laws administered by the Food and Drug Administration (FDA). This paper focuses on these considerations by discussing the definition of a food additive, the FDA's regulatory framework for substances used in food-contact articles, and the parameters used for testing the materials to establish their FDA status. The paper also examines emerging regulatory concepts being developed at the FDA, and presents an overview of the data necessary to support a Food Additive Petition submitted to clear a new food-contact material. The evaluation of food-contact materials involves legal, regulatory, and scientific considerations; this paper concentrates on the scientific and technical considerations. Although legal definitions and regulatory concepts are discussed, these will receive only a cursory treatment. A more exhaustive discussion of the pertinent legal concepts can be found elsewhere (1).

KEYWORDS: Additives, FDA, food, migration, regulations, specifications.

Background

The technical considerations for evaluating food-contact materials are dependent not only on scientific principles, but also on the FDA's regulatory framework. To provide a basis for discussion of the regulatory considerations, a brief review of the applicable legal definitions and concepts governing the use of such materials is appropriate.

Section 409 of the federal Food, Drug, and Cosmetic Act (the Act) prohibits the use of a food additive unless the additive is used in conformity with a food additive regulation. Food additive is defined in Section 201(s) of the Act as "any substance the intended use of which results, or is reasonably expected to result, directly or indirectly, in its becoming a component or otherwise affecting the characteristics of any food." The term clearly includes not only substances that are intentionally added to foods, such as sweeteners and flavors, but also those that are not intentionally added but come into contact with and are reasonably expected to migrate to food. The latter, the so-called indirect food additives, are a major focus of this paper.

However, not all materials contacting food are food additives. Some substances that are not considered additives are also not subject to FDA regulation as such. These substances fall into three categories: prior-sanctioned, generally recognized as safe (GRAS), or not reasonably expected to become components of food.

Prior-sanctioned means that the substance can be used in accordance with a specific sanction or approval granted by an FDA or U.S. Department of Agriculture (USDA) letter or memorandum written prior to the enactment of the Food Additives Amendment in 1958. Unfortunately, no master list exists for the materials covered.

Many substances enjoyed a long history of safe use prior to the enactment of this amendment. These materials were, thus, deemed GRAS. Since 1958 additional substances have been considered GRAS. However, the substances listed in the regulations by no means constitute all GRAS substances.

The last category of food-contact materials not considered additives are those not reasonably expected to become components of food. These may be so used without specific regulatory FDA approval or clearance. However, consideration of this concept requires additional attention regarding analytical method sensitivity.

When the Food Additives Amendment was enacted in 1958, analytical methods were generally capable of reliably determining substances at concentrations of a few parts per million (ppm). At that time, 1 ppm was a rea-

Borodinsky is a staff scientist at Keller and Heckman, 1001 G St. NW, Washington, DC 20001.

I. FDA's Conditions of Use

Condition	Description
A	High temperature heat-sterilized (e.g., over 212°F)
B	Boiling-water sterilized
C	Hot-filled or pasteurized above 150°F
D	Hot-filled or pasteurized below 150°F
E	Room temperature-filled and stored (no thermal treatment in the container)
F	Refrigerated storage (no thermal treatment in the container)
G	Frozen storage (no thermal treatment in the container)
H	Frozen or refrigerated storage: Ready-prepared foods intended to be reheated in the container at time of use

sonable sensitivity to use when determining if a substance should be considered a food component.

However, while the law remained unchanged, analytical chemistry has made great advances since 1958. Shortly after the enactment of the amendment, the ability to detect lower concentration levels began to raise more questions about what is considered reasonably expected to become a component of food. To provide some guidance, a paper was presented by the FDA in 1969 at the National Technical Conference of the Society of Plastics Engineers. Often referred to as the Ramsey Proposal (named after its author, Lessel Ramsey), it would have permitted by regulation the use, without the prior promulgation of an applicable food additive regulation, of substances that migrate to food in quantities no greater than 50 parts per billion (ppb). This regulation would have applied to all substances except those known to pose special toxicological concerns. Although never formally adopted by the FDA, the proposal's standards are still deemed scientifically valid.

Since 1969 we have relied on the Ramsey Proposal in establishing the appropriate analytical method sensitivity used to determine whether a substance used in a food-contact article is reasonably expected to become a component of food. The 50-ppb sensitivity is considered a suitable benchmark in those cases where the substance would not pose a public health concern, or where the use of the substance is not expected to result in wide consumer exposure, such as in a container for milk or a carbonated beverage. In cases of toxicological concern or substances with wide consumer exposure, a method sensitive to 10 ppb or less is recommended. Carcinogens, heavy metals, pesticides, and other highly toxic substances obviously require separate study.

The FDA is now moving toward adoption of a "threshold-of-regulation" policy with respect to food-contact materials. Under this policy, the Administration is expected to take the position that certain food-contact substances may be exempt from the full review process in those cases in which available data indicate the potential for dietary exposure to those substances is extremely low *(2)*. For example, when considering a substance for which no toxicological data are available, the presence of the substance at levels no greater than approximately 0.5 ppb should require no regulatory action *(3)*. If safety data are available and indicate no health or safety concern, it may be possible to establish a threshold at exposure levels somewhat above 0.5 ppb.

Extraction testing

Compliance testing vs. migration testing

The food additive regulations clear substances on a generic basis (i.e., based on chemical identity) rather than on a proprietary basis and often impose specifications to establish food-grade standards for the materials. These compliance specifications often take the form of extraction testing. However, it is only coincidence that some tests used to determine compliance with a regulation, often referred to as "end tests," are similar to the more rigorous tests that establish substance migration into food.

The compliance specifications, outlining relatively easy and rapidly performed tests, are similar to quality control specifications. These tests are usually of short duration (generally less than two hours, although occasionally as long as 48 h) and typically only require gravimetric analysis for total migration. The results are used to determine whether the material or article passes a given specification and are not intended for assessing dietary exposure.

Migration testing, on the other hand, is intended to simulate the intended conditions of package use. This type of testing, typically conducted over a longer period (10 days or more) than the compliance testing, virtually always requires analysis for one or more specific potential migrants. The results are used to determine whether a substance (either resin or adjuvant) is expected to become a component of food and is therefore subject to the FDA's jurisdiction as a food additive. If the substance is found to migrate, the results can be used to ascertain its contribution to the human diet.

Although the two types of testing are conducted under different conditions and are analyzed differently, they often have a common reference point—the FDA's model of Conditions of Use, tabulated in Title 21, Section 176.170(c) of the Code of Federal Regulations (see **Table I**). The severity of a compliance test is often keyed to this table; the end test for paper and paperboard components is such an example. In addition, this testing scheme was used as a basis for migration testing in the FDA's *Recommendations for Chemistry Data for Indirect Food Additive Petitions*, issued in September 1988. Because of this common reference point, the two types of testing are often incorrectly viewed as being interchangeable.

The type of testing needed depends on the purpose to which the testing results will be applied. If a substance is specifically listed in a food additive regulation and testing is needed to determine compliance with the regulation, the end test must be satisfied. In this case, migration testing using the FDA's *Recommendations* does not determine whether the material meets the specification unless a correlation between the specification and the migration test results has been established.

If, on the other hand, a substance is not listed and a determination is needed on whether the substance may reasonably be expected to migrate to food, migration testing simulating the intended conditions of use is needed. In this case, specification testing is irrelevant.

Migration testing

There is a logical approach to establishing the FDA status of food-contact material. The first and most important step is to completely identify the substance and its intended condition(s) of use. This identification serves as the basis for the rest of the evaluation process. If the substance is specifically cleared by a food additive regulation, if it is GRAS for its intended use, or if its use is the subject of a prior sanction or approval, it may be used without prior action by or consultation with the FDA, provided it meets any necessary compliance specifications or tests.

If, however, there is no applicable clearance for the substance, appropriate extraction studies must be designed and performed to simulate and, to some extent, exaggerate the intended conditions of use. The relevant parameters to be considered in designing the necessary migration tests are summarized below.

Extraction samples. The extractions may be performed using actual articles, portions cut from the articles (e.g., container walls), or test plaques. If test plaques are prepared, they should have a minimum thickness of 0.020 in. If the substance is an adjuvant material added to a polymer or paper, it should be present at the highest anticipated use level. A sufficient number of samples and controls should be prepared to permit replication of the analyses and to provide reliable results.

Solvents. Because analyses of actual foods may be difficult, the FDA recommends the use of food-simulating solvents. The use of 8% ethanol as an appropriate simulant for aqueous, acidic, and low alcohol-content foods (up to 13% ethanol) is recommended.

To simulate fatty foods, the FDA's primary recommendation is an edible oil such as corn oil or olive oil; as an alternative, synthetic triglycerides such as HB307 may be used. Another suitable alternative is Miglyol 812, a fractionated coconut oil (fatty acids composed of 55% C_8 and 45% C_{10}). If the use of a liquid fat poses analytical problems, an aqueous alcohol solution may be used as an alternative solvent. Depending on the nature of the substrate to be tested, the FDA recommends either 50% ethanol or 95% ethanol as an appropriate solvent.

Volume-to-surface ratio. If actual articles will be extraction tested, they should be filled with the test solvent to the typical commercial level. If test plaques are used, the solvent volume-to-surface area ratio should reflect that of the article. As an alternative, 10 mL/in.^{2} can be used; this is a general FDA recommendation. Other ratios may be appropriate, e.g., when testing substances in repeat-use articles.

Time/temperature. The FDA recommends that testing be conducted under the most severe use conditions. A frequently used listing of common use conditions encountered in food packaging is shown in Table I.

The FDA's recommended testing is performed by combining in one procedure the testing conditions that simulate expected shelf life. Short-term accelerated testing at 120°F is considered to adequately simulate migration that may occur over an extended period of time at room temperature. **Table II** is a summary of the FDA's recommended general extraction testing conditions used to simulate the tabulated conditions of use. It is important to realize that this summary is general and is not intended to cover all possibilities. For example, other testing conditions are appropriate for repeat-use articles, for some paper and paperboard articles, for microwaveable trays, and for oven-use trays.

Analytical methodology. The extracts should be analyzed at the end of the test period for the migrant(s) of interest. Any suitable analytical procedure can be used to determine whether the substance is extracted by the test solvent. However, the analytical method should be capable of detection at the appropriate sensitivity, as discussed above. In the event that a method cannot reach this level of sensitivity directly, the sensitivity may be improved, for example, by evaporating the ethanol extracts to dryness, dissolving the solid residue in a small amount of solvent in which these analytes are highly soluble (e.g., methylene chloride), and analyzing the resulting concentrated solutions for the presence of the analyte.

II. FDA's general extraction testing conditions

Condition of use	*Test conditions*
A	250°F for 2 h + 120°F for 10 days
B	212°F for 2 h + 120°F for 10 days
C	Fill at 212°F, then hold at 212°F for 30 min + 120°F for 10 days
D	Fill at 150°F, then hold at 150°F for 30 min + 120°F for 10 days
E	120°F for 10 days
F	70°F for 10 days
G	70°F for 5 days
H	212°F for 2 h

Validation. The methods of analysis must be validated to ensure that any work-up procedure does not affect the analysis and that other substances present in the extract do not interfere with the analysis. To validate an analytical method, a control sample (i.e., one without the subject substance) can be extracted under the same conditions of time and temperature and with the same solvent as the test samples. After removing the sample, the solvent should then be spiked by adding the potential migrant(s) at a level equivalent to the detection limit. The solvent is then evaporated and worked up following the same procedure used for the sample. Alternatively, extracts obtained from replicate samples exposed to the same conditions of time and temperature, and exposed to the same solvent as the test sample, should be spiked with the analytes after removal of the sample and worked up following the same procedure. For nondetected analytes, validation requires that the added analyte be detected (quantitative recovery is not required) when it is known to be present by spiking at a level equivalent to the detection limit.

If the analyte is found when the samples are tested, validation requires spiking to be conducted at three levels: at one half the quantity found, at approximately the quantity found, and at about two times the quantity found. In this case, recoveries should be reasonably quantitative and approximately linear to validate the procedure.

Report. A report should be prepared describing the samples used in the test, the analytical method used, and data obtained, including any data used to calibrate the method. The report should also contain copies of appropriate instrumental output.

The petition process

If it is determined that an additive is not currently regulated, GRAS, or prior-sanctioned, and that the additive may be expected to migrate to food under the conditions of use, Section 409(b) of the Act permits petitioning the FDA to issue a regulation prescribing the conditions under which the additive may be safely used. The Act sets forth the information required to support a Food Additive Petition, and the procedures and substantive parameters to be followed by the FDA in considering a petition. These information requirements and procedures are spelled out in greater detail in Part 171 of the food additive regulations.

Reduced to its fundamentals, a Food Additive Petition must describe a product, identify and estimate the quantities of any substances that will enter the diet, and demonstrate that these quantities are safe. Thus, there are several categories of information that must be supplied to the FDA to clear the use of a material in food-contact applications: (a) the composition and method of manufacture for the substance, (b) its intended conditions of use, (c) the quantity of the substance likely to become a component of food under the intended conditions of use, (d) an estimate of the concentration of the additive in the human diet, and (e) any toxicology data relating to the safety of the intended use. In addition, information on the potential environmental impact of the manufacture, use, and disposal of the material must be submitted.

Identity of the food additive

A Food Additive Petition requires detailed information about the identity and composition of the product and how it is made. The petition should include the product's structural and molecular formulas, Chemical Abstracts Service registry number and name, as well as other names (including the trade name by which the product is known), and an analytical method that may be used to identify the substance. Any appropriate manufacturing specifications for the product should also be provided to show that adequate quality control procedures have been developed. These specifications should primarily relate to the identity, purity, and safety of the product rather than to its technological utility and may include, for example, values of minimum percent purity and/or limits on specific impurities such as by-products and unreacted starting materials.

Amount of food additive proposed for use

The FDA requires petitioners to describe the conditions under which the additive will contact food and to provide data on the quantity of substances likely to become components of food under the use conditions. Information on the product's conditions of intended use should include identification of the concentration at which the material will be used, time and temperature conditions of use, and the types of food contacted. In the case of a polymer adjuvant, such as an antioxidant, the identity of the polymers in which it will be used is also needed. Identifying the exact conditions of use is a prerequisite to establishing specific extraction protocols used to determine the extent to which the product is likely to migrate to food in various applications.

Extraction study data

The same testing protocol that determines whether a substance will migrate to food under the use conditions is pertinent for acquiring the extraction data to support a Food Additive Petition. If, for example, detectable levels of a substance are found to migrate in an extraction test, the same data should be included in a petition.

Amount of additive entering the diet

If migration of uncleared substances is expected based on the extraction studies, the amount of extractable species expected to enter the human diet, referred to as the estimated daily intake (EDI), should be calculated. This value is based on the amount of additive expected to migrate to food and the approximate fraction of the daily diet considered by the FDA to contact the material.

The intake of the additive is expressed as a fraction of the overall human diet. The EDI is obtained by dividing the fractional intake the average daily intake of food, which is assumed to be 3000 g (including all liquids ingested). These calculations invariably represent a worst-case estimate of the dietary intake of the additive because they assume that the additive always migrates at the maximum levels found in the extraction studies, and that all food-contact materials of a given type are made using the substance of interest.

Intended physical or technical effect

With regard to the product's intended technical effect, the FDA merely requires that the petition list some useful properties of the substance. Any available technical literature may be submitted for this purpose. If possible, some data substantiating the technical properties should be given along with a copy of the test method used to develop the data.

Analytical procedure

The petition should provide an analytical procedure for determining whether the product complies with applicable composition or use level restrictions. Thus, if limits are proposed for the levels of specific components of a polymer, or if a maximum concentration of an adjuvant substance in the finished food-contact material is specified, methods for ensuring compliance with these limits must be supplied along with data demonstrating the validity of the methods.

Safety of the additive

Depending on the identity and quantity of material that migrates, toxicology data may be required. These data can be in the form of studies undertaken by the petitioner or existing studies in the literature. The extent of toxicology required to clear a given substance depends on the nature of the material and the EDI for the substance, as determined from the extraction study.

In general, if the dietary concentration of an additive is less than 50 ppb, the FDA requires only an acute toxicity study in rats. If the intake of the additive is above 50 ppb and below 1 ppm, two 90-day feeding studies, one performed in a rodent species (usually rats) and one in a non-rodent species (usually dogs) are necessary. In addition, in this intake range the agency generally requires an *in utero* stage in the rat study, which involves exposing unborn rats to the substance. Finally, if the dietary intake of the additive is above approximately 1 ppm, the FDA requires a full panoply of studies including two-year feeding studies, multi-generation reproductive studies, and other toxicological tests. These are usually prohibitively expensive for indirect additives, and can be avoided in most instances with suitably designed and executed migration studies that limit the intended use.

Environmental assessment

Finally, the FDA requires an analysis of the potential environmental impact of the production, use, and disposal of the additive. This analysis should include information on waste materials resulting from the manufacture, use, and disposal of the additive. In particular, the petition should identify any waste streams produced by manufacture of the additive, the methods of treatment and disposal, and the quantities of substances ultimately released. The petition should also provide an estimate of the anticipated annual production volume for food-contact applications. Finally, the petition should list any federal, state, or local environmental or occupational regulations affecting the manufacturing site, including emission, effluent, and workplace exposure limits applicable to specific substances used or produced during manufacture of the material. Copies of pertinent plant operating permits, which demonstrate regulatory compliance, must be provided. If available, information on the environmental fate of released substances, as well as data on the toxicity of these substances to water-, air-, or land-dwelling organisms, should be submitted.

Further considerations

The Center of Food Safety and Applied Nutrition determines if adequate data have been submitted with a petition. The management and review of petitions are handled by various divisions within the Office of Pre-market Approval. Once a substance is formally listed by the FDA in a food additive regulation, that clearance applies to any product meeting the specifications and use limitations found in the clearance. Unlike the licensing scheme used to provide drug and medical device approvals, food additive clearances apply generically to any product meeting the requirements of an applicable regulation. ■

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