A new era in the regulation of food-contact materials was ushered in by the Food and Drug Administration's (FDA) implementation, in January 2000, of the Food Contact Notification (FCN) system.

Prior to the advent of this program, made possible by Congressional passage of a major change in the governing legislation, the only means for bringing about explicit FDA clearance for food-contact substances was the submission of a food additive petition or Threshold of Regulation request. With respect to Food Additive Petitions, although the statute required FDA to review petitions within 180 days, lack of agency resources extended review time to an average of two to four years. While Threshold of Regulation exemptions took less time to obtain, they were only given for food-contact substances upon a showing that the dietary concentration of the substance would not exceed 0.5 parts per billion (ppb)\(^1\). The FCN system, on the other hand, is applicable to all food-contact materials. Notifications become effective in 120 days, thereby allowing the submitter to market its product in a time frame that is much more consistent with current global marketing requirements.

Although it is now possible to obtain explicit clearances for food-contact materials within a more reasonable amount of time, manufacturers are still free to determine for themselves whether a particular product complies with the Federal Food, Drug, and Cosmetic Act (FD&C Act). Indeed, there are many situations where it is unnecessary and ill advised to approach the agency. Leading food and drug attorneys have long advised against seeking the agency’s sanction, when marketing without it is equally legal.\(^2\)

It would appear quite logical, therefore, to begin this analysis of the application of the law to food packaging materials by restating the available alternatives to obtaining explicit FDA clearance for food-contact materials.\(^3\) Thereafter, as there are many situations where explicit FDA clearance is necessary or desirable, we discuss the true administrative law sea change that the Food and Drug Administration Reform Act of 1997 (FDAMA) set in motion by authorizing the Food Contact Notification system. We conclude with a description of the FCN program and a guide for submitting notifications.

I. Alternatives to Obtaining Explicit FDA Clearance

A. Background - Definition of a Food Additive

FDA has authority over food packaging or processing equipment materials only to the extent that they are encompassed by the definition of a "food additive" under the FD&C Act.\(^4\) Section 201(s) of the act defines a food additive as:

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\text{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 . . . packing, . . . packaging, . . . or holding food . . .).}
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The definition specifically excludes substances that, when used as intended, are (1) not reasonably expected to become a component of food;\(^5\) (2) generally recognized as safe (GRAS) among experts qualified by scientific
training and experience to evaluate their safety; or (3) used in accordance with a sanction or approval issued prior to 1958 by either FDA or the U.S. Department of Agriculture (USDA) ("prior-sanctioned").

Under the definition, the term "food additive" includes not only substances directly added to food, but also substances—such as some packaging or processing equipment materials—that contact food and the components of which are reasonably expected to migrate to food, unless those substances are GRAS or prior-sanctioned. If a substance that is reasonably expected to become a component of food is not GRAS or prior-sanctioned, the statute now provides that its use for food-contact applications must be authorized by an effective Food Contact Notification or a food additive regulation, or be the subject of a "Threshold of Regulation" exemption letter.

B. "No Migration"/"No Food Additive" Determination

The "food additive" definition in the FD&C Act indicates that a satisfactory regulatory status for a substance may be established based upon a determination that the substance is not reasonably expected to become a component of food. This determination, often referred to as the "no migration" exemption, is the most significant escape clause, for it provides the most-used premise for self-determination that a food packaging material need not be subjected to FDA's review.

While FDA has not provided definitive criteria for determining at what point a substance may reasonably be expected to become a component of food, there are, nonetheless, sources of guidance for such a determination. Two key sources of guidance are the 1969 Ramsey Proposal and the 1979 Monsanto v. Kennedy decision, upon which industry, with FDA's knowledge and tacit consent, has come to rely.

The Ramsey Proposal was a draft notice of proposed rulemaking circulated by FDA in 1969 in response to widespread criticisms offered by the food packaging industry. Named for its author, Dr. Lessel Ramsey, then Assistant Director of Regulatory Programs at FDA's Bureau of Science, the proposal urged sanctioning the use of substances migrating to food in quantities no greater than 50 parts per billion (ppb) without requiring an applicable food additive regulation. This proposal would have applied to all food-contact substances except those known to pose some special toxicological concern—for example, heavy metals and known carcinogens—or substances shown to produce toxic reactions at levels of 40 parts per million (ppm) or less in the diet of man or animals. Although never formally adopted by FDA, this concept has received wide acceptance in the scientific community.

The second source of guidance is the U.S. Court of Appeals for the District of Columbia Circuit's opinion in Monsanto v. Kennedy. In Monsanto, FDA argued that any contact of a substance with food may be expected to result in some transfer of the substance to the food, with the conclusion that FDA could require a food additive clearance for every food-contact material, even without evidence that the substance migrates to food. In rejecting FDA's argument, the D.C. Circuit explained:

Congress did not intend that the component requirement of a "food additive" would be satisfied by . . . a mere finding of any contact whatever with food . . . . For the component element of the definition to be satisfied, Congress must have intended the Commissioner to determine with a fair degree of confidence that a substance migrates into food in more than insignificant amounts.

Id. at 955. Stated another way, a food-contact substance must be expected to become a component of food in more than a toxicologically insignificant amount to be properly considered a food additive.

Since 1979, FDA has cited Monsanto as support for decisions that go so far as to permit putative carcinogenic substances to remain on the market where the substances have been found to present insignificant risks to health. This was evidenced by FDA's decision to continue to permit the use of methylene chloride for decaffeinating coffee on the basis that "the risk from the use of methylene chloride in decaffeinating coffee (no
greater than 1 in 1 million) is so small as to be effectively no risk. FDA's use of the de minimis concept for substances it has characterized as carcinogens is a clear indication that the agency tacitly approves of no-migration determinations since it follows easily that any minute, undetected quantities of toxicologically innocuous indirect additives migrating to food must certainly be considered of de minimis public health significance.

How does one determine with confidence that a substance may not reasonably be expected to become a component of food in more than insignificant amounts? There are several ways to make such a determination, each of which involves the use of migration data or diffusion calculations.

The most time-honored and, therefore, most common approach requires conducting extraction studies in accordance with the FDA guidelines for the preparation of petition or notification data. Specifically, if extraction studies simulating the intended conditions of use demonstrate that the test substance does not migrate to food-simulating solvents when the solvents are analyzed with a method of appropriate sensitivity, the substance may not reasonably be expected to become a component of food. For most substances, if the extraction study does not detect the substance in food (or a simulating solvent) using an analytical sensitivity level of 50 parts per billion (ppb), a finding of "non-detected" is reasonable. For certain applications where the packaged food is consumed in large amounts so that dietary exposure is expected to be high—for example, beverage containers—a lower level of analytical sensitivity for detection, such as 10 ppb, is recommended.

In the absence of extraction studies, it may be possible to calculate that a substance is not a food additive either by using a "worst case" assumption of 100 percent migration of the substance to food and demonstrating that the projected dietary intake would be insignificant, or by applying diffusion principles to show that the substance would not be detected if a method of appropriate analytical sensitivity were properly applied. Whether the basis is migration testing data or valid calculations, a finding that a substance is not detectable in food with a method of appropriate analytical sensitivity permits the conclusion that the substance may not reasonably be expected to become a component of food and, therefore, may be marketed without any formal FDA clearance or notification.

For substances known to pose special toxicological concerns, such as heavy metals or carcinogenic "constituents" (substances that may be starting materials, or processing chemicals, but are not the additive as it contacts food), the use of lower detection limits both in calculations and in extraction studies is indicated. The proper lower detection limits must be determined on a case-by-case basis considering the nature of the material, its intended conditions of use, and, if available, any official "virtually safe dose" arrived at by FDA or any other government agency.

C. Functional Barrier Doctrine

A subset of the "no migration" exclusion is the functional barrier doctrine. This concept dictates that if a substance is not part of the food-contact surface of a package and is separated from the food by a barrier that prevents migration of the substance to food, then the substance may not be expected to become a component of food and, thus, is not a food additive within the meaning of the FD&C Act. Whether a true functional barrier exists may be determined simply by considering the package structure and the exposure conditions anticipated for the package or, in more complex applications, by conducting calculations or migration testing. This approach is often useful in determining the regulatory status of interior layers of laminates, outer layers of packages, and external printing inks.

The doctrine was a well-established, though unpublished, FDA position before being acknowledged in the 1975 case of Natick Paperboard v. Weinberger. In this case, the U.S. Court of Appeals for the First Circuit cited the applicability of the functional barrier principle while addressing the issue of whether polychlorinated biphenyl (PCB) contaminants were impermissible food additives. The court stated that if "the food placed in or to be placed in the paper container is or will be insulated from PCB migration by a barrier impermeable to such
migration, so that contamination cannot reasonably be expected to occur, the paperboard would not be a food additive. In other words, substances separated from food by a functional barrier are not food additives.

D. GRAS Substances

Substances properly deemed generally recognized as safe (GRAS) are excluded from the definition of "food additive" and, thus, are exempt from the premarket clearance requirement that applies to food additives. Section 201(s) defines a GRAS substance as one that is


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.

A list of substances deemed GRAS by FDA is set forth at 21 C.F.R. Parts 182, 184 and 186. However, the agency acknowledges in Section 182.1 that this list is not exhaustive, stating that "[i]t is impracticable to list all substances that are generally recognized as safe for their intended use." Thus, manufacturers are free to determine on their own whether a substance is generally recognized as safe by qualified experts without FDA approval or notification.

FDA has published regulations describing eligibility requirements for GRAS substances at 21 C.F.R. § 170.30. General recognition of safety requires a "common knowledge" about the substance throughout the scientific community knowledgeable about the safety of substances directly or indirectly added to food. For substances not widely used in food prior to 1958, general recognition of safety based on "scientific procedures" requires the same quantity and quality of scientific evidence as are required to bring about approval of a food additive regulation, or in the case of a food-contact substance, an effective Food Contact Notification for the ingredient. General recognition of safety ordinarily is based on published studies that may be corroborated by unpublished studies and other data and information.

The presence of substances at extremely low levels in the diet may be considered generally recognized as safe in specific instances. Supporting this conclusion, a panel of renowned independent experts convened by the Canadian Center for Toxicology (CCT) concluded that substances present in the diet at concentrations of 1.0 ppb or below can be considered safe even if no toxicity testing has been performed on the specific chemical, provided that there is no reason to believe that the substance demonstrates unusual toxicological properties. For substances with some toxicity data that indicate a lack of genotoxic potential, a higher level may be determined safe based upon classical toxicological principles as outlined in various regulatory guidelines. Based on the principles discussed in the Canadian report, it is reasonable for a company to take the position that low levels of nontoxic substances may be considered GRAS in certain applications.

FDA's "Threshold of Regulation" rule provides additional support for the proposition that substances can be considered safe on the basis of low dietary exposure. The Threshold Rule is related to the "no migration" exception, in that it represents the agency's determination of a de minimis dietary level for food-contact materials, where the potential threat posed from migration of the substance is so slight as to obviate the need for regulation of the substance as a food additive. Specifically, it enables the agency to exempt from regulation those food-contact substances that are not known carcinogens upon a showing that the dietary concentration of the substance does not exceed 0.5 ppb. The rule also exempts those substances already regulated as direct food additives that, when used as intended in food-contact applications, do not present a dietary exposure in excess of 1 percent of the acceptable daily intake established for the substance's direct addition to food. The exemption is applicable so long as the substance does not contain any carcinogenic constituents or impurities with a TD₅₀ of less than 6.25 mg/kg body weight per day.
In adopting the Threshold of Regulation Rule, FDA acknowledged the right of a manufacturer to determine independently that a substance used in a particular application does not make the substance a food additive, but FDA reserved to itself the authority to issue a formal Threshold of Regulation exemption. Meeting the criteria of the Threshold of Regulation, it is submitted, provides a sound basis for determining that a substance is generally recognized as safe when used as intended.

More recently, three well-respected officials at FDA’s Center for Food Safety and Applied Nutrition published a paper providing a scientific basis for an expanded threshold scheme. The chemists examined data on 709 carcinogens listed in the Carcinogenic Potency Database (CPDB) compiled by Gold et al. and found that the structure of an untested substance can be a strong indicator of whether it is likely to be a carcinogen. Further, results of short-term toxicity data and genotoxicity tests, i.e., Ames assays and LD_{50} tests, can be strong indicators of carcinogenic potency.

As a result of their findings, the chemists concluded that the dietary threshold could be expanded to as high as 15 ppb for certain substances, depending on the structure of the substance and available toxicity data. Specifically, the authors recommended the following tiered threshold scheme:

1. A dietary threshold of 4 ppb - 5 ppb for (a) those substances lacking structural alerts (i.e., those substances not belonging to the following structural classes of substances known to be carcinogens: N-nitroso compounds, strained heteronuclear rings, alpha-nitro-furans, polycyclic amines, hydrazines/triazenes/ azides/azoxy compounds, organophosphorous compounds and heavy metal-containing compounds), regardless of the results of an Ames assay; and (b) those substances with structural alerts other than N-nitroso and benzidine-like compounds testing negative in the Ames assay.

2. A dietary threshold of 10 ppb – 15 ppb for those substances testing negative in the Ames test and having an LD_{50} above 1000 mg/kg.

While the threshold scheme discussed in the Cheeseman paper does not represent the promulgation of new threshold criteria by the agency, it provides further guidance for the private sector's evaluation of food-contact materials. Indeed, it may be cogently argued that it provides a suitable basis for taking self-determined GRAS positions for dietary exposures at levels higher than 0.5 ppb, or even 1 ppb, for substances that qualify under the analysis set forth in the paper.

E. Prior-Sanctioned Substances

The prior-sanctioned exclusion, like that for GRAS substances, is drawn directly from the FD&C Act. Prior to the Food Additives Amendment of 1958, FDA and USDA received many inquiries from manufacturers regarding the suitability of using a particular substance in food or as a component of a food-contact material. With the enactment of the 1958 Amendment, the agencies’ responses to these informal inquiries attained the status of de facto regulatory exemptions, because the FD&C Act excludes from the definition of "food additive" any substance that is the subject of one of these "prior sanctions." As in the case of GRAS substances, there are many more prior-sanctioned substances than are listed in FDA’s regulations or files.

The prior-sanctioned status of a substance is a straightforward question of fact that depends solely on the existence of an appropriate pre-1958 letter. This does not mean FDA is powerless to control prior-sanctioned substances. The agency has attempted to limit the scope of the exclusion by consistently construing prior sanctions as narrowly as possible. Though FDA is precluded from regulating a prior-sanctioned substance as a food additive, the agency can prohibit or set conditions on the use of any substance which it has proof is adulterating food. Proof is the critical word, for in a case of alleged adulteration, the government must prove that the amount of the substance getting into food is such that the food may be injurious to health within the meaning of Section 402(a)(1) of the FD&C Act.
F. Housewares Exemption

The status of a food-contact substance under the FD&C Act and FDA's regulations depends not only on the chemical formulation of the material, but also on its specific applications and the conditions of its intended use. In this regard, a substance used in contact with food as part of a product that may properly be characterized as a "houseware" is exempt from the requirement for premarket clearance by FDA as a food additive. A houseware is generally considered to be an article that is used by a consumer (and, at least in some circumstances, a commercial establishment) to hold, prepare or serve food.

Although the "housewares exemption" was not written into the statute, the legislative history of the 1958 Amendments explains that Congress did not intend FDA to have premarket clearance authority over housewares when it authorized the agency to regulate food additives. During the Congressional hearings that preceded passage of the Food Additives Amendment of 1958, the Honorable John Bell Williams, Chairman of the House Subcommittee on Health and Science and the floor manager of the bill, specifically stated that the legislation was "not intended to give the Food and Drug Administration authority to regulate the use of components in dinnerware or ordinary eating utensils." 34

At a Food and Drug Law Institute Conference in 1958, shortly after passage of the legislation, an FDA panel recognized the housewares exemption. The panel, which received written questions from the floor, responded to the following questions as indicated:

Question --

Does the Food Additives Amendment of 1958 require pretesting of containers that are not intended for the commercial packaging of foods, but that are used for:

(A) Dispensing?
(B) Preparing or serving?
(C) Temporary one-time use?

Examples are:

(A) Paper cups used in soft-drink or coffee dispensers.
(B) Baby bottles, cooking utensils, refrigerator bowl covers, plastic tableware.
(C) Plastic or paper plates and eating utensils intended for picnic use.

Answer --

The amendment was not intended to cover the containers listed as examples as they are used in the home, the restaurant, or beverage dispensers. However, if such a container were used as a package for food being merchandised in a retail market, we think it could very well become subject to the amendment.

Since 1958, FDA, on occasion, has confirmed in public statements that components of dinnerware, eating utensils, and other kitchenware used to prepare or serve food by individual consumers fall under the "housewares exemption" to the FD&C Act. For example, Dr. Patricia Schwartz, Regulatory Policy Strategic Manager at FDA’s Center for Food Safety and Applied Nutrition, reaffirmed the housewares exemption, citing cookware, dishes, and cutlery as examples in a 1992 speech comparing U.S. and European Union (EU) regulation of food-contact materials. 35 Additionally, in its booklet titled Requirements of Laws and Regulations Enforced by the U.S. Food and Drug Administration, FDA states that housewares are not subject to regulation as food additives. 36
The housewares exemption from the premarket clearance requirement is based on the recognition that such products generally do not give rise to any public health concern. Of course, the adulteration provisions of Section 402(a)(1) of the FD&C Act still apply to housewares, and FDA will take action against housewares that may adulterate food. Therefore, it remains the responsibility of producers of housewares to take every reasonable precaution to ensure that their products are suitable for use with food and will not create a health hazard under the intended conditions of use.

**G. Mixture Doctrine**

The "mixture doctrine," as it has come to be known informally, permits manufacturers to physically blend discrete substances if the respective substances are separately cleared by FDA for the intended application. Under this doctrine, such blends require no further FDA clearance provided that each substance in the mixture complies with any limitations applicable to the substance in its respective regulation. If there is a chemical reaction between the combined substances, as opposed to only a physical mixing, the reaction has resulted in a new substance requiring its own regulatory clearance, and the mixture doctrine does not apply.

It is important to note that any limitations, such as extractives limitations, relating to the individual components of a mixture are properly applied to the relevant individual components rather than to the mixture. However, limitations relating to end-use application of the mixture, such as food-type or temperature limitations, or extractable limitations on the finished food-contact article, must be applied to the mixture as a whole. The mixture is subject to the most restrictive end-use limitations applicable to any of the components.

**H. Basic Polymer Doctrine**

FDA stated many years ago that a "basic resin" is the product that results when a polymerization process has been carried to commercial completion. Substances such as catalysts, chain regulators, chain transfer agents, and other materials used at low levels (generally 1 percent or below) and required to produce the resin are considered part of the basic resin and are not subject to independent regulatory consideration. Thus, the clearance afforded the basic resin subsumes a clearance for those substances that are necessarily used during the polymerization stage to produce it. This principle is often referred to as the Basic Resin Doctrine.

The Basic Resin Doctrine merely reflects the practical reality that FDA cannot write generic regulations for food packaging materials that specifically clear every substance that might be a trace component or contaminant of packaging materials as a result of every manufacturing process that yields a suitable resin. Thus, where a substance is used during polymerization in small quantities and either becomes a part of the resin thus formed or is otherwise removed from the resin at the conclusion of polymerization, its potential for migration is minimal; there is no reasonable expectation of migration and, therefore, the substance is not considered a food additive. Since trace quantities of these "unregulated" substances are not perceived to present a public health hazard, FDA has chosen not to subject the substances to the burdensome premarket clearance provisions of Section 409 of the FD&C Act that apply to food additives.

**II. The Food Contact Notification System**

Until early in 2000, if a substance used in a food-contact application was not already regulated under a specific provision in 21 CFR § 170 et. seq. or was not covered under one of the exemptions or exclusions described in the preceding sections of this article—or if the manufacturer simply wished to have evidence of some official FDA acceptance of its product for corporate or customer assurance purposes—the manufacturer or some other interested party was required to file a Food Additive Petition. Then, there would likely be a wait for an average of two to four years for the government to promulgate and publish a formal Food Additive Regulation. With the enactment of the Food and Drug Administration Modernization Act of 1997 (FDAMA), the new Food Contact Notification (FCN) system was developed and FDA began to implement it at the beginning of the new century.
It should be clearly understood and recognized that the advent of this new system does not abrogate the right to rely on the existing Food Additive Regulations or any of the enumerated exemptions or exclusions, since the new law simply added another clearance option, albeit one that FDA has indicated that it favors for food-contact substances. Under the FCN system, manufacturers can file a Food Contact Notification instead of a Food Additive Petition with FDA; the most noteworthy characteristic of such a notification is that it becomes effective in 120 days by operation of law unless formal substantive objections are interposed by the agency. While FDA has reserved the right to insist on the filing of Food Additive Petitions in a few exceptions discussed below, almost all food-contact substances qualify for the FCN treatment. In light of the importance of this change, and prior to detailing what is required in a proper FCN, there follows first a brief discussion of the reason the new system is characterized as a "sea change."

A. The Fundamental Change In Policy That the FCN System Signals

The passage of Section 309 of the Food and Drug Administration Reform Act of 1997 and the advent of the FCN system constituted a dramatic shift of course in the regulatory atmosphere. It opened the door for FDA to deal much more promptly with an embarrassing number of pending Food Additive Petitions that had occupied its time being called to task by a Congressional Committee, and set the stage for a reordering of priorities that could only benefit the public, industry, and the agency. The hearings that ultimately led to enactment of the legislative amendment to the food additive provisions in the Federal Food Drug and Cosmetic Act of 1938, also gave rise to the suggested change in the system for regulating so-called "indirect additives" by highlighting the fact that FDA was being called upon to spend inordinate amounts of time and resources on a once-postulated potential hazard that time had shown was virtually no hazard at all.

As is discussed in a bit more detail in the next section, the new system is one that relieves the agency of the need for spending enormous amounts of time on regulation writing and internal clearances. This is all to the good. Less obviously, it provides industry with a method for meeting the government's and the public's need for being assured that a material can be safely used without having to suffer the kind of delays that can make it impractical to market a good product, even some that could go a long way toward helping protect against scourges such as the microbiological contamination of foodstuffs.

For the legal community and students of regulatory policy, one other point is worthy of mention: The new FCN system, with its 120-day deadline for government objections and requirement that the objections, if any, be substantive and subject to appeal, reverses the regulatory momentum. Heretofore, those who wished to clear new substances had no choice other than to wait for data to be evaluated at FDA's leisure, regulations to be drafted and circulated, and sign-off to be given by an estimated 20 to 40 agency staffers. No wonder average clearance times of two to four years were required for packaging materials, and much more for direct additives. Moreover, the only legal remedy available to try to force government action was to seek a mandatory injunction to require the agency to comply with the 180-day time limit given it to act on food additive petitions. Since all the courts could do would be to order FDA to act on a petition, no such suits for injunctions were ever submitted, it being obvious that they could not force a constructive result and might do just the opposite. Now, however, at least in the case of food-contact substances, the leverage has shifted; FDA knows it must make decisions in 120 days unless the notifier has agreed to some other arrangement, and the agency has graphically demonstrated that it can complete the necessary reviews and clear notifications in a timely way.

Also for those with an interest in regulatory philosophy and policy, it should be duly noted that a very likely reason for the agency's good record on notification action is the fact that what needs to be done—i.e., sound scientific review and evaluation of well defined facts—can and is being done, and the bureaucratic requirements that do nothing for public health have been largely eliminated by doing away with the need for writing generic regulations that demand a lot of guessing about how substances might be used. There may well be some lessons here for other situations where delays are progress-killing and clearances can be proprietary and more narrowly—but much more promptly—given. Substituting generic regulation writing for licensing may sound like an appealing idea—as it did to the agency authors of the Food Additives Amendment of 1958—but in practice, the
licensing concept is apt to be more precise and functional. FDA's experience with food-contact substance regulation already has demonstrated this point.

Under the FCN program, a manufacturer or supplier of a food-contact material may submit a notification to FDA regarding the identity and use of a new food-contact substance, along with information supporting the conclusion that the substance is safe for the intended use. Companies may begin marketing the new food-contact substance, or materials made with it, 120 days after filing the notification, unless the agency determines that, based on the information and data submitted in connection with the notification, such use has not been shown to be safe or the agency requires submission of a Food Additive Petition to ensure public safety. Unlike food additive regulations, and in a throwback to the "no objection" letters issued by the agency prior to 1958, notifications may be relied upon only by the submitter and its customers.

1. Administration of the Program by FDA

Within approximately 30 to 60 days of the filing of an FCN, FDA will provide the submitter with a letter acknowledging receipt of the submission. In this acknowledgment letter, FDA also will provide a description of the substance that it believes the notification will cover, any applicable specifications for the substance and limitations on use, the party it recognizes as the notifier and/or manufacturer of the substance, and the date on which the notification will become effective (assuming no objection is filed). This provides the submitter with an opportunity to ensure that FDA understands the terms of the notification and to request any necessary modifications.

Once the notification becomes effective, FDA will include it in a list of effective notifications, which can be found on its Web site at: http://vm.cfsan.fda.gov/~dms/opa-fcn.html. At present, FDA is updating the list approximately twice a month. In addition, FDA has been providing letters to submitters confirming that their notifications have become effective. The letter and the Web site listing should be sufficient to assure customers of the satisfactory status of the relevant product.

FDA has issued draft guidance documents and published proposed regulations to implement the notification program. The guidance documents describe the chemistry and toxicology data needed to submit a complete notification and the administrative information required. Copies of the current drafts of these documents are available on the FDA Web site at http://www.fda.gov/.

2. Requirements for an FCN

The requirements for an FCN are substantially similar to those for a Food Additive Petition. An outline of the information that is usually needed to file an acceptable FCN follows:

a) Composition and Method of Manufacture

An FCN must include complete information regarding the identity and composition of the food-contact substance and how it is produced. To satisfy this requirement, information on the substance's chemical name, structure, and molecular formula, including its Chemical Abstract Service (CAS) Registry Number, is essential. In addition, analytical data will be needed that may be used to identify each substance e.g., a typical infrared spectra.

Manufacturing specifications for the substance must be provided to show that adequate quality-control procedures have been developed. These specifications should relate primarily to the identity, purity, and safety of the product rather than to its technological utility; they may include, for example, values for minimum percent purity and/or limits on specific impurities such as byproducts and unreacted starting materials. Other specifications may also be included. The results of quality-control tests of several lots of material (at least three) should be submitted to demonstrate the ability to produce the additive within the specified parameters.
Although such data are recognized as proprietary, and are kept confidential by FDA, FCNs must include a description of the manufacturing process, including a list of the reagents, solvents, catalysts, purification aids, etc., used in the manufacturing process, the relevant amounts used, and the manufacturer's (or supplier's) specifications for these materials. Copies of any methods used to verify compliance of the reagents with their specifications also should be included. Care should be exercised to impress upon FDA the necessity and propriety of keeping this type of manufacturing information securely confidential.

**b) Intended Conditions of Use**

FDA requires that FCN submitters describe the conditions under which an additive will contact food, and provide data on the quantity of any substance likely to become a component of food under the intended conditions of use. Information on the conditions of intended use should include the concentration of the food-contact substance in the final food-contact material, temperature of use, and the types of food contacted.

It has been said frequently (and wisely) that there are no more important words in all of food and drug law than "intended conditions of use." This is because no other factor has as much to do with the cost and degree of difficulty in bringing about a satisfactory regulatory status for a substance. The intended conditions of use of a substance will determine the anticipated exposure, whether it is to be dietary or otherwise, and hence, will dictate the level of toxicology data necessary to establish its safety. In turn, what toxicology is needed will impact tremendously on the cost of bringing a product to market, and on the time it will take to make marketing a realistic possibility. This determination can have tremendous impact on whether the product is worth the effort and cost needed to clear it.

One other aberrational effect, at least as the authors of this article see it, is that if the intended use dictates the need for a chronic feeding study, for example, or if FDA receives a two year study it has not previously evaluated as part of a filing, it is entitled under its guidance document and proposed rules to insist that a substance be the subject of a Food Additive Petition instead of a food contact notification so that it will have more than 120 days of review time. We characterize this as aberrational because, it is submitted, this same objective, i.e., more review time, can more sensibly be accommodated by submitting the longer studies to the FDA staff for review and comment prior to filing an FCN, and not filing until the data is deemed acceptable for the purpose. It is not in the best interests of FDA or industry to insist that petitions be filed simply to give the agency more time to review data if this can be accomplished in the more practical way suggested here. Using the pre-filing review and then the notification system will still conserve a substantial set of resources by eliminating the need for writing and clearing the art form known as regulation writing.

While FDA has no power to deny or delay clearance of any food additive or food-contact substance because of doubt about its utility or efficacy, it may deny clearance of a notification or a regulation if the product will be used to promote consumer deception or fraud. Hence, the agency requires that the FCN describe the purpose for using the substance. Available technical literature on the additive may be submitted for this purpose. If possible, some data should be given substantiating the technical properties along with a copy of the test method used to develop the data. Further, the FCN should provide an analytical procedure for confirming that the product complies with any applicable composition or use level restrictions.

**c) Amount of Additive in Food and Entering the Diet**

Another most critical aspect of a FCN concerns the amount of the additive expected to enter the human diet. FDA's determination of the safety of the additive is based on a comparison of the dietary exposure to available toxicity data. The dietary concentration can be calculated by multiplying the amount of the additive expected to migrate to food by the approximate fraction of the daily diet expected to contact materials containing the additive. Where the additive is expected to contact different food types, the Estimated Daily Intake (EDI) is calculated using a weighted average of the applicable migration levels that relates to the amount of a food type that is expected to contact a particular type of packaging material. The EDI is calculated by multiplying the
dietary concentration by the average daily intake of food, which is assumed by FDA to be 3,000 grams (including all liquids ingested). These calculations invariably represent a conservative estimate of the dietary intake of the additive because they are based on the assumption that the additive will always migrate at the maximum levels found in the extraction studies, and that all food-contact materials of a given type will be made using the subject substance.

One notable difference between petitions and FCNs is the new responsibility placed on notifiers to calculate the cumulative estimated dietary intake (CEDI) of potential migrants. The proponent of an FCN will need to estimate the CEDI from all sources of exposure, rather than just the EDI from the use that is the subject of its notification. FDA is compiling its own estimates of CEDIs, beginning with the most widely used substances, and intends to make this information publicly available, probably through the FDA Web site. In the meantime, the required CEDI data can be requested from the agency on a case-by-case basis.

d) Safety of the Additive

The type of toxicology data required to clear the proposed use of a given substance will depend on the nature of the material and the CEDI for the substance. In this regard, there is a difference between the data requirements for notifications and what was required for petitions filed in the earlier years. For substances with CEDIs under 0.5 ppb, the toxicology data requirements remain unchanged, i.e., no toxicology data is required, although relevant data must be submitted if available. However, for exposures between 0.5 ppb and 50 ppb, two genotoxicity studies (a bacterial mutagenicity assay plus an in vitro cytogenetic damage or mouse lymphoma assay) are needed. These studies replace FDA's former requirement for petitions of an acute toxicity study (LD$_{50}$). The rationale for this change is that for substances entering the diet at these minute levels, acute toxicity almost never is a concern (that is, virtually nothing will be acutely toxic at low parts-per-billion levels). On the other hand, it is possible, at least in theory, for carcinogenic effects to be elicited at low dietary levels; hence, the toxicity endpoint of greatest concern for low-exposure substances is carcinogenicity. The now-recommended genotoxicity screening assays are intended to provide an indication as to whether a given substance is likely to be a carcinogen.

Where the intake exceeds 50 ppb but is below 1 ppm, a third genotoxicity study (in addition to the two noted above) in the form of an in vivo chromosomal aberration study is recommended, as well as two subchronic (90-day) studies (one in a rodent and one in a non-rodent animal) as historically required for these exposures.

For food-contact substances that may be present in the diet at a level in excess of 1 ppm, a full range of toxicity studies is generally required, including chronic (two-year) toxicity/carcinogenicity studies in rats and mice, a one-year feeding study in dogs, and multi-generation reproductive studies in rats. (Where cumulative dietary exposure exceeds this 1 ppm level, FDA is recommending the filing of a Food Additive Petition instead of a FCN). The required data can be studies undertaken by the FCN submitter, or existing studies in the open literature, where available and applicable to the intended use.

The level of safe intake of the additive is determined by the lowest "no-observed effect level" (NOEL) established in the feeding studies. If two subchronic (but not two-year) studies have been conducted, FDA typically divides the lowest NOEL by a factor of 1000 to yield the "acceptable daily intake" (ADI), the highest intake level that may be cleared based on the available data. When chronic feeding studies have been conducted the NOEL is divided by 100 to determine the ADI. (FDA does not determine an ADI based on acute toxicity data; generally, the agency merely determines that intake below 50 ppb is "negligible" and, thus, that extensive toxicity data are not required to establish safety.)

e) Environmental Assessment (EA)

The National Environmental Policy Act (NEPA) requires any federal agency to assess the potential environmental impact of actions that it takes. FDA has long considered this requirement to apply to its
promulgation of regulations in terms of clearing food additives, and believes that such information also needs to be submitted for notifications. As a result, FDA requires information to be submitted that assesses potential environmental impact so that the agency can make a finding of no significant impact, or, if needed, complete an environmental impact statement.

With respect to Food Additive Petitions, FDA promulgated a regulation that categorically exempts from the environmental assessment requirements substances that constitute less than 5 percent of the food-contact article, provided that the substances are intended to remain with the finished packaging material through use by consumers, and are substances that are used in articles intended for repeated use.

Likewise, the agency has published a rule regarding categorical exclusions for EAs for FCNs. It announced that all of the categorical exclusions that previously applied to Food Additive Petitions will also apply to FCNs. For those notifications that do not qualify for a categorical exclusion, EAs must be submitted to provide potential environmental impact information on the use and disposal of the food-contact substance.

### III. Conclusion

As explained above, the new FCN program holds the promise of allowing manufacturers to obtain explicit FDA clearance for their products within a relatively short amount of time. However, the exclusions and exemptions discussed in the opening parts of this paper will continue to remain important since, when applicable, they can open the door for immediate marketing even in cases where a supplier ultimately wishes to submit a Food Contact Notification for customer assurance or other internal purposes.

1. See 21 C.F.R. § 170.39 (setting the Threshold of Regulation for substances used in food-contact articles).

2. A highly respected fellow member of the food and drug law bar, and a former General Counsel of FDA, advised in 1969 that:

[I]t is the primary and initial responsibility of the manufacturer of a product to determine the proper classification of this product, and to make certain that it meets all applicable legal requirements. It is in no instance necessary, and in most instances inadvisable, to ask the Food and Drug Administration for its opinion on the proper jurisdiction over the product . . . . [It] will probably seize upon any opportunity to state that the product should be handled as a [food additive]. It is therefore usually preferable for the manufacturer to exercise the obligation of proper classification given to him by the statute, rather than abdicating that responsibility to the Government.

Address by P.B. Hutt, *Proper Classification of Products Under the Federal Food, Drug, and Cosmetic Act*, presented at the Annual Convention of the Federal Bar Ass'n, Miami, Fla. (Sept. 4, 1969). This paper dealt with cosmetics and drugs for the most part. With Mr. Hutt's permission, the bracketed [food additive] has been substituted for the word "drug."


5. *Id*.

6. *Id*.

7. Prior to 1958, FDA and USDA received numerous inquiries from manufacturers regarding the suitability of using a particular substance in food or as a component of a food-contact material. With the enactment of the 1958 Food Additives Amendment, the agencies' responses to these informal inquiries attained the status of *de facto* regulatory exemptions, because the FD&C Act excludes from the definition of "food additive" any substance that is the subject of one of these prior sanctions.

8. The "Threshold of Regulation" rule enables FDA to exempt food-contact materials, on a case-by-case basis, from the requirement that each be cleared by an applicable food additive regulation. See 21 C.F.R. § 170.39; 60 Fed. Reg. 36,582 (July 17, 1995) (describing the Threshold of Regulation as the "process for determining when the likelihood or extent of migration to food of a substance used in a food-contact article is so trivial as not to require regulation of the substance as a food additive").


11. 50 Fed. Reg. 51,551 (1985). See also FDA's discussion of its determination of safety in connection with the issuance of the following final rules permitting the use of various indirect additives which, in one way or another, involved the use of non-functional carcinogenic constituents: 65 Fed. Reg. 68888 (2000), 65 Fed. Reg. 3384 (2000), and 60 Fed. Reg. 54425 (1995); and *Scott v. FDA*, 728 F.2d 322 (6th Cir. 1984), where the court upheld FDA's decision to clear the use of D&C Green No. 5 based on its finding that the presence of a carcinogenic constituent created no reasonable risk of harm to individuals exposed to the color additive that has not itself been shown to cause cancer.


14. The "virtually safe dose" represents the dietary concentration of a carcinogen which, if consumed daily over a person's lifetime, is estimated to result in a worst-case risk of one in 1 million.

15. See, e.g., letter from Frederick A. Cassidy, FDA, to the author (June 9, 1965).

17. *Id.* at 1107-08.

18. 21 C.F.R. § 182.1.

19. See 21 C.F.R. § 170.30(b).

20. See *id*.


23. See *id*.

24. See *id*. (describing the Threshold of Regulation as the "process for determining when the likelihood or extent of migration to food of a substance used in a food-contact article is so trivial as not to require regulation of the substance as a food additive").

25. See *id*. TD50 is the calculated dose that causes cancer in 50 percent of the test subjects.

26. See *id*.

27. See M.A. Cheeseman *et al.*, *A Tiered Approach to Threshold of Regulation*, 37 Food and Chemical Toxicology 387 (1999).


29. More specifically, the authors found that most carcinogens can be grouped into one of the following seven classes of substances: *N*-nitroso compounds, strained heteronuclear rings, alpha-nitro-furans, polycyclic amines, hydrazines/triazenes/ azides/azoxy compounds, organophosphorous compounds, and heavy metal-containing compounds.

30. The LD$_{50}$ is defined as the dose that induces death in 50 percent of dosed animals.


35. P. Schwartz, "Regulation of Food Packaging in the EEC and the U.S.: A Comparative Analysis" (1992). In this speech, Dr. Schwartz stated:
FDA has traditionally not regulated "housewares" as food additives. Articles like cookware, dishes, and cutlery used exclusively in the home for food preparation and storage have not been subject to the pre-market safety evaluation to which commercial food packaging is subject. This does not mean that these "housewares" are not regulated at all by FDA. The Agency can still take action with respect to a "houseware" under the General Safety Clause (Sec. 402) of the Federal Food, Drug, and Cosmetic Act, but the burden of proof is on FDA to demonstrate that the food contacted by the "houseware" has been adulterated.


38. This issue does not arise in the same context with respect to Food Contact Notifications, since FDA receives all the information it needs about the manufacture of the substance at hand in the notification and does not need to write a regulation giving a generic clearance. The later substitution of reaction control agents other than those identified in the notification must be evaluated on a case-by-case basis. Unless the change is apt to alter the character of the substance or result in significant migration of uncleared substances to food, the effective notification should remain satisfactory.

39. See Food Additives: Hearings on Bills to Amend the Federal Food, Drug, and Cosmetic Act with Respect to Chemical Additives in Food Before a Subcomm. Of the House Comm. On Interstate & Foreign Commerce, 85th Cong. 44 (1958) [hereinafter Food Additives Amendment Hearings]. For a comprehensive detailing of what was wrong with the basic system put into play by the Food Additives Amendment of 1958 and how the system came to be administered in ways that added to its defects, see Heckman, Jerome The Food Additives Amendment of 1958, It's Time for a Change in the Law, FDLJ, 1966; considerable discussion of the legislative and regulatory history of the amendment also is set forth in Fathoming, supra note 3.

40. See id. at 447 (testimony of Jerome H. Heckman, Society of the Plastics Industry).

41. During a seminar held 10 months after the FCN program was instituted, FDA's Dr. Mitchell Cheeseman reported that of the 83 FCNs that had been received and reviewed by the agency, 73 had become effective, with an average agency review time of 113 days. Address by Mitchell Cheeseman, Ph.D., The Food Contact Notification Program, presented at Keller and Heckman LLP's Seminar Getting Through FDA's New Food Contact Notification Process (November 2000).


43. See id.

44. See Heckman, Jerome H. and Mathew, N. Ajoy, Does FDA Have the Power to Demand Efficacy Data to Clear Food Additives?, July 1999 (http://www.khlaw.com/; also on file with author).


46. This change did not occur as a result of the change in the regulatory system. In a real sense the shift was a
coincidental event, in that the Division of Health Effects and Evaluation of the Center for Food Safety and Nutrition had already moved away from accepting LD₅₀ data and, instead, began demanding the genotoxicity studies when the petition effort was winding down and the FCN program was being commenced.

47. As previously stated, it is submitted that this is unnecessary unless the interested party insists on petition treatment and is unwilling to wait to file a notification until after the agency has been given a reasonable time to review a longer-term toxicity study. The better approach would seem to be to work with the agency to allow it the time to review the data and then file a notification, rather than to go through the other delays a petition always involves.


49. See 21 C.F.R. § 25.32.


51. See id. at 30367.