in focus

Polymer colorants and antimicrobial food additives

A look at the complexities of food contact notifications

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Food contact colorants and antimicrobial food additives present unique challenges for manufacturers seeking regulatory compliance. Food contact notifications for polymer colorants typically require complicated chemical analysis and safety assessment due to the potential for multiple impurities. Antimicrobial food additives are regulated by different jurisdictions and identifying the correct regulatory pathway can be challenging. In this paper, TSG Consulting's Leslie Patton, PhD, Senior Scientific Consultant, provides an overview of the Food Contact Notification (FCN) program and identifies how to navigate the complexities of polymer colorants and antimicrobial food additives.

Novel polymer colorants and antimicrobial food additives are challenging from a notifier's perspective.

Initial challenges

Colorants are regulated as food contact substances (FCS) by the US Food & Drug Administration (FDA), and new colorants can be brought to market through FDA's Food Contact Notification (FCN) program. As with all FCS, polymer colorants used in food packaging must be characterized chemically and evaluated for safety. Polymer colorants often require rigorous chemical analysis that can be complicated by multiple impurities, all of which must be identified, quantified, and assessed for safety.

Antimicrobial food additives may be regulated by multiple agencies, including the FDA, US Environmental Protection Agency (EPA) and the US Department of Agriculture (USDA), depending on their intended use. Most food contact antimicrobials are regulated by both FDA under the Federal Food Drug & Cosmetic Act (FFDCA) and EPA under the Federal Insecticide Fungicide and Rodenticide Act (FIFRA). USDA's Food Safety Inspection Service (FSIS) has additional jurisdiction over antimicrobials applied to meat and poultry carcasses.

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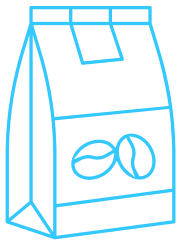

Overview of the FCN Program

FDA regulates colorants and antimicrobial food additives through the FFDCA and the subsequent Food and Drug Administration Modernization Act of 1997 (FDAMA). FDAMA established the Food Contact Notification program, which has become the primary method for authorizing new food contact substances. A FCS can be defined as any substance that is intended for use as a component of materials used to manufacture, pack, package, transport or hold food if such use of the substance is not intended to have any technical effect in the food.

For whom is an FCN effective?

The notifier is typically the manufacturer or supplier of the FCS. A notification is only effective for the specific manufacturer or supplier listed on the notification. If a company wants to purchase and use an existing FCS that is already the subject of a notification, they may only do so if the notification is effective for the same conditions as their intended use. If their intended use is different, they must notify FDA with their own FCN.

What information must be included in an FCN?

An FCN comprises information on the chemistry, toxicity and environmental effects of the FCS and must include the following:

1. Chemical identity
2. Intended conditions of use
3. Manufacturing process
4. Intended technical effect
5. Dietary exposure estimate
6. Comprehensive toxicological profile (CTP) and safety determination
7. Environmental impact

After submission

Data are compiled for each of these sections and submitted as attachments to FDA Form 3480. Once submitted, the FDA Center for Food Safety and Applied Nutrition (CFSAN) acknowledges the receipt of the FCN. The Notification is considered effective 120 days after that time unless the Agency requests more information or clarification. Typically, a notifier has 10 days to respond to such a request. After receiving the notifier's response, the Agency can take additional time to review the material; therefore, the overall review time may exceed 120 days. Notifiers are informed by FDA when it is satisfied with the revisions and the FCN is effective. It often takes six to eight weeks from this time to see the new FCN in FDA's online inventory of effective food contact substance notifications.

What are food contact substances?

Food contact substances may be indirect food additives like polymers, monomers, adjuvants, coatings, and adhesives. They may also be food processing agents like boiler water additives, ion exchange resins, or antimicrobial agents used in the processing of vegetables, meat and fish.

FDA accepts paper or electronic FCN submissions. CFSAN has recently begun to accept FCNs through its online portal, the CFSAN Online Submission Module (COSM).

Complicated cases: polymer colorants

What is a colorant?

Colorants are dyes, pigments, or other substances that impart color or alter the color of a food contact material without having any technical effect on the food itself. Colorants that have been cleared by the FDA for use in food contact polymers are listed under 21 CFR §178.3297. In general, colorants must not be used excessively; only utilize what is reasonable to accomplish the intended coloring for the food contact material.

The challenge

Polymer colorants are typically chemical mixtures, so identifying all components can be a challenge. Notifiers must carry out chemical analysis using validated techniques to establish the colorant's chemical identity. Concentrations of all major impurities with supporting analytical data and calculations must be provided in the FCN. Impurities can include residual starting materials, including all reactants, solvents, and catalysts, as well as by-products and degradation products.

Notifiers are likely to need a migration study to quantify a colorant's potential dietary exposure. The migration study requires thorough analysis of all substances and detailed documentation of analytical method validation.

The following parameters should be documented to validate all analytical methods:

1. **Accuracy:** Reflects that the concentration measured is consistent with an accepted refence value. Includes fortification and recovery
2. **Precision:** Accounts for variability of data under testing conditions
3. **Specificity:** Relates to the identification of a certain substance amongst other components
4. **LOD (Level of Detection):** The lowest concentration of the analyzed substance that can be reliably detected above the 'blank'
5. **LOQ (Level of Quantitation):** The lowest concentration of the analyzed substance that can be reliably determined quantitatively
6. **Linearity:** The ability of the method to produce results that are proportional to the concentration of substance being analyzed

Notifiers must submit representative spectra or chromatograms which inform the analysis. Some examples of appropriate techniques include nuclear magnetic resonance (NMR) and ultraviolet (UV)-visible or atomic absorption spectroscopy (AAS).

Additionally, specifications are critical in identifying and demonstrating control of impurity levels (e.g. carcinogenic contaminants) and physical properties of the colorant. Specifications ensure that the food contact substance, when tested, will be equivalent to that which is introduced into commerce.

Toxicological perspectives on FCS including colorants

CFSAN uses a tiered approach to determine toxicology testing requirements that is dependent on the cumulative dietary exposure to a substance:

1. **0.5 parts per billion (ppb) or less:** No toxicity tests required
2. **Greater than 0.5 ppb and not exceeding 50 ppb:** Genetic toxicity tests in bacteria and mammalian cells are required
3. **Greater than 50 ppb and not exceeding 1 part per million (ppm):** The following tests are required: genetic toxicity tests in bacteria and mammalian cells, an *in vivo* test for chromosomal damage, and two subchronic tests to determine an Acceptable Daily Intake (ADI) for the FCS/ impurity
4. **Equal or greater than 1 ppm:** FDA normally requires a Food Additive Petition (FAP) instead of an FCN

In the Comprehensive Toxicological Profile (CTP) section of the FCN, notifiers must consider and discuss the potential carcinogenicity of the FCS and any impurities. If any data gaps exist, structural analysis of the compound should be undertaken. Any alerts to genotoxicity or carcinogenicity must be detailed in the CTP. The CTP should reach a conclusion on potential carcinogenicity of each substance discussed. If a component is identified as potentially carcinogenic, the notifier should perform a cancer risk assessment. If the cancer risk is negligible for carcinogenic impurities, its use may be approved.

Complicated cases: antimicrobial food additives

What is an antimicrobial food additive?

Antimicrobial food additives are used to control bacteria, viruses, fungi, protozoa, and other microorganisms in or on food or food contact articles.

The challenge

Antimicrobial food additives are regulated by multiple federal agencies. Understanding the intended use and technical effect of the substance is the key to determining how they are regulated and whether an FCN is even necessary. FDA regulates the following uses, at least in part:

1. Antimicrobials used directly in or on food: Includes sanitizing solutions for beef, poultry, fish, eggs, or produce that is processed or intended for further processing (e.g. canning, freezing, cooking, pasteurization or homogenization, irradiation, milling, grinding, chopping, slicing, cutting or peeling). FDA has dual jurisdiction over those food additives used in the production of meat and poultry and some egg products with the USDA Food Safety Inspection Service (FSIS).

3. Food-contact substances (other than components of food packaging) with no intended ongoing effect on the food contact article: Includes production aids used to control the growth of microorganisms in the equipment and materials used to manufacture food contact articles. These FCSs do not need to function in the finished article, though they may become a component of the finished article during production and therefore can migrate into food. Examples include papermill slimicides and preservatives used in the production of adhesives and coatings.

2. Food-contact substances (other than components of food packaging) intended to have an ongoing effect on any part of the article except the food-contact surface: Refers to a materials preservative, which is a FCS used to protect the food contact material from microbial damage (e.g. discoloration, degradation). These are not intended to kill microbes contacting the finished article like a surface sanitizing solution would, but rather to preserve the article itself. An example is an antimicrobial incorporated into a polymer used to make food contact articles such as food processing equipment.

4. Antimicrobials included in, or applied to, food packaging with or without an ongoing antimicrobial effect: Includes sanitizing solutions intended for use on food packaging, aseptic packaging, and antimicrobials impregnated into food packaging to protect the package. Note that if the substance is intended to affect the food itself, such as to extend the shelf life of food, it is regulated as a food additive rather than an FCS.

Who has jurisdiction?

For antimicrobial food additives used on meat, poultry and certain egg uses, FDA and FSIS have separate regulatory responsibilities that must be satisfied before the additive may be legally marketed. Under the Federal Meat Inspection Act (FMIA) and the Poultry Products Inspection Act (PPIA), FSIS has authority over the suitability of food ingredients, including antimicrobials and/or sources of radiation used in meat and poultry processing plants.

While the FDA has regulatory discretion over the antimicrobial food additive uses described on the previous page, these products may also be subject to the Federal Insecticide Fungicide and Rodenticide Act (FIFRA) administered by US EPA and require registration as pesticides. Examples of such antimicrobial products include those used to treat process water in food processing facilities or raw agricultural commodities during transportation to food processing facilities (number one on page 7). Likewise, products like pulp and paper mill slimicides and material preservatives (numbers 2 and 3 on page 7) require pesticide registration with EPA.

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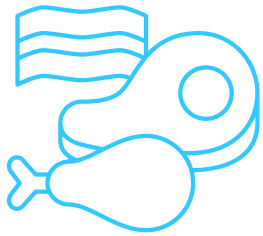

Testing of antimicrobial food additives

Selecting an appropriate testing method requires an understanding of how the antimicrobial food additive will interact with the food matrix. Given the variability of food matrices, FDA does not have a single performance standard for antimicrobial food additives. It has, however, published an online version of its Bacteriological Analytical Manual to enable notifiers to select a suitable protocol from its preferred laboratory procedures. FDA requires that testing results reveal a measurable difference between treated and untreated controls.

FSIS also maintains a Microbiological Laboratory Guidebook[1] detailing current protocols for analytical tests covering meat, poultry and egg products. Like with FDA, no specific test is prescribed, and methods are not confined to just agency-recommended laboratory protocols.

1Microbiology Laboratory Guidebook by USDA Food Safety and Inspections Service https://www.fsis.usda.gov/wps/portal/fsis/topics/science/laboratories-and-procedures/guidebooks-and-methods/microbiology-laboratory-guidebook/microbiology-laboratory-guidebook

Achieving a successful FCN

Food contact notifications for novel uses of polymer colorants and antimicrobial food additives are complicated in their own respective ways. Colorants require sufficient data through meticulous laboratory testing for identification of all substances and impurities in the mixture while, antimicrobial food additives can be regulated across multiple jurisdictions. Understanding the final use and effect of the antimicrobial determines how it is regulated.

For a notifier to be successful, a firm understanding of chemical identity and safety is required. Understanding how a substance will ultimately be used determines the potential exposure in people's diets and is key to determining product safety. The availability and presentation of this information to FDA is paramount to achieving a successful notification.

How TSG can help

TSG's consultants have a wide range of experience with food contact notifications to the FDA. We can assist with the:

- Preparation and submission of Food Contact Notifications (FCN) and other submissions related to food contact materials
- Development of food additive petitions
- Preparation of GRAS notices/assessments, convene expert panels
- Creation of dietary exposure models
- Determination of FCS compliance with regulations in 21 CFR

For guidance on submitting Food Contact Notifications, contact TSG at:

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We serve a number of key markets and industry sectors including agricultural, industrial, consumer, food and beverage, animal health, and medical. Our teams comprise scientists and regulatory experts – many of whom have previously held positions at regulatory agencies, departments, and in industry.

This combination of science, regulatory expertise and knowledge of how institutions and industry operate provides our clients with superior and well-rounded guidance. TSG Consulting has offices in France, Germany, Spain, UK, USA and Canada. TSG is a Science Group (London listed) company.

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