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September 2007

Guidance for Industry

Microbiological Considerations for Antimicrobial Food Additive Submissions

DRAFT GUIDANCE

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For questions regarding this draft document contact the Center for Food Safety and Applied Nutrition (CFSAN) at 301-436-1226.

U.S. Department of Health and Human Services
Food and Drug Administration
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Guidance for Industry^[1]

Microbiological Considerations for Antimicrobial Food Additive Submissions

This draft guidance, when finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call the appropriate telephone number listed on the title page of this guidance.

I. INTRODUCTION

The Food and Drug Administration (FDA) is responsible for prescribing the conditions of safe use of food additives under section 409 of the Federal Food, Drug, and Cosmetic Act (the Act). To evaluate the safety of food additives and determine their conditions of safe use, the agency

uses the food additive petition (FAP) process and the food contact notification (FCN) process. In addition, FDA may, upon request, exempt from regulation as a food additive those substances used in food-contact articles (also known as food contact substances) that migrate into food at levels that are below the threshold of regulation (TOR). This guidance is directed at questions regarding microbiological data requirements for FAPs, FCNs, and TOR requests that are unique to the use of antimicrobial food additives and food contact substances. This guidance will assist petitioners and notifiers in designing studies to determine whether an antimicrobial food additive achieves its intended technical effect. Also, this guidance discusses microbiological data that may be necessary to demonstrate that an antimicrobial agent will be safe for the intended use.

This guidance applies to all FAPs, FCNs and TOR requests where the food additive is intended to control microbes in or on food. This includes sources of radiation for treating food. However, it is important to note that the U.S. Department of Agriculture (USDA) Food Safety and Inspection Service (FSIS) is responsible for determining the suitability of food additives in meat and poultry products; according to FSIS, “*suitability* relates to the effectiveness of the substance in performing the intended technical purpose of use, at the lowest level necessary, and the assurance that the conditions of use will not result in an adulterated product or one that misleads consumers.”^[2] FSIS derives its authority to regulate the suitability of food additives in meat and poultry from the Federal Meat Inspection Act (FMIA) and the Poultry Products Inspection Act (PPIA), respectively. FDA and FSIS currently have a Memorandum of Understanding (MOU) regarding each agency's responsibilities in the evaluation and approval of food ingredients and sources of radiation used in the production of meat and poultry products. In accordance with this MOU, FDA will collaborate with FSIS on any antimicrobial food additive submission to FDA involving meat or poultry.

Given the complexity and variety of antimicrobial products and the diverse conditions of use, no single document can anticipate and address all microbiological issues. Therefore, this guidance is intended to answer common questions associated with microbiological data requirements for FAPs, FCNs, or TOR requests for antimicrobial food additives so that meaningful and sufficient data are provided with each submission. It is intended to assist developers of antimicrobial agents for use in or on food in providing evidence to support their intended uses. FDA recommends that petitioners and notifiers discuss with the agency any proposed studies prior to their initiation to ensure that these studies will address FDA's safety concerns. In addition, FDA recommends that submitters meet with the agency prior to the submission of a petition or notification to prevent an expenditure of resources on activities that may not provide adequate data.

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

II. QUESTIONS AND ANSWERS

A. What is and is not a food additive?

The term “food additive” is defined in section 201(s) of the Act. The first part of that section states that a food additive is 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, producing, manufacturing, processing, preparing, treating, transporting, or holding food; and including any source of radiation intended for any such use. Section 201(s) goes on to expressly exempt from the definition of food additive certain categories of substances, including substances that are “generally recognized as safe” or “GRAS” for the intended use. A partial list of substances recognized by FDA as GRAS may be found in 21 CFR Part 182, and a list of substances affirmed by FDA as GRAS appears in 21 CFR Part 184. These lists may include substances which are GRAS for use as antimicrobial agents.

“Pesticide chemicals,” as defined at section 201(q) of the Act, are exempt from the definition of a food additive. Pesticide chemicals and pesticide chemical residues in or on food must conform to a tolerance, or an exemption from tolerance, established by the Environmental Protection Agency (EPA) under section 408 of the Act.

For the complete definition of a food additive and the exemptions, see section 201(s) of the Act.

B. What is an antimicrobial food additive?

The term “antimicrobial food additive,” as used in this guidance, refers to a substance or a source of radiation that meets the food additive definition and is used to control microorganisms such as bacteria, viruses, fungi, protozoa, or other microorganisms in or on food or food contact articles.

C. What is FDA’s regulatory authority with respect to antimicrobial food additives?

FDA is the primary Federal agency responsible for ensuring the safety of food additives. Under section 409 of the Act, all food additives are subject to review and approval by FDA before they can be marketed in the United States. This guidance applies to FAP, FCN, and TOR submissions. Food additives that are intended to have a technical effect in food are authorized through the petition process prescribed in section 409 of the Act. The standard that FDA applies to determine whether the intended use of a food additive is safe is reasonable certainty of no harm (see 21 CFR 170.3(i)). For food additives demonstrated to FDA to be safe under the intended conditions of use, FDA will issue a regulation that specifies the conditions of safe use. The food additive regulations are codified in 21 CFR parts 172-180 and may be obtained from the Internet by searching the current edition of the CFR. Part 172 lists food additives for direct addition to food, part 173 lists food additives used during food processing, and parts 174-178 list food additives used in food packaging and other food contact articles. Approved sources of radiation for inspecting and treating food are listed in 21 CFR part 179. Food additives permitted in food or in contact with food on an interim basis pending additional study are listed in 21 CFR part 180.

Food additives that are intended for use as a component of materials used in manufacturing, packing, packaging, transporting, or holding food, if such uses are not intended to have any technical effect in food, are considered food contact substances (see section 409(h)(6) of the Act). As a result of the FDA Modernization Act of 1997, the primary method for authorizing new uses of food contact substances is the FCN process (see section 409(h) of the Act). In the case of a food contact substance, FDA will allow a notification for the subject food contact substance to become effective prescribing the conditions under which a food additive may be safely used. The standard used to establish the safety of a food contact substance is the same as that for any other food additive (i.e., reasonable certainty of no harm). More information on this process is available from the Food Contact Substance Program website. A current Inventory of Effective Food Contact Substance Notifications is found on the CFSAN Internet.

In addition, under 21 CFR 170.39, FDA may, upon request, exempt from regulation as a food additive food contact substances that become a component of food at levels below the threshold of regulation. Such a request is commonly referred to as a threshold of regulation (TOR) submission. More information on the TOR submission process is available in Guidance for Industry: Submitting Requests Under 21 CFR 170.39 Threshold of Regulation For Substances Used in Food-Contact Articles. A current inventory of Threshold of Regulation Exemptions issued by FDA is available on the CFSAN Internet. The data requirements for a TOR submission are the same as those for a FAP or FCN and the safety standard that FDA applies is the same.

For a detailed discussion of FDA's regulatory authority over antimicrobial food additives, see FDA's Guidance to Industry entitled, *Antimicrobial Food Additives – Guidance*. It is important to note that, depending on the proposed use, an antimicrobial food additive may also be a pesticide under the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA). As such, it may be subject to registration as a pesticide by the EPA as well as regulation as a food additive.

D. What is FDA's regulatory authority with respect to requesting microbiological data?

Microbiological data may need to address certain issues raised by the findings that FDA makes under section 409 of the Act. Several are described below.

- Under section 409(c)(3)(B) of the Act, a food additive regulation will not be established if an evaluation of the data “shows that the proposed use of the food additive would promote deception of the consumer in violation of [the] Act or would otherwise result in adulteration or in misbranding of food within the meaning of the Act.” Here, the microbiological data may be used to demonstrate that an antimicrobial agent does not promote consumer deception, such as making a food product appear to be fresher or of greater value than it actually is.
- Under section 409(c)(4) of the Act, if “a tolerance limitation is required in order to assure that the proposed use of an additive will be safe, the Secretary shall not fix such a tolerance limitation at a level higher than he finds reasonably required to accomplish the physical or other technical effect for which such additive is intended; and, shall not establish a regulation for such proposed use if he finds upon a fair evaluation of the data before him that such data do not establish that such use would accomplish the intended physical or other technical effect.” When a tolerance limitation is required, the

microbiological data may be used to demonstrate that an antimicrobial agent achieves its intended technical effect and that the maximum permitted use level is not higher than what is reasonably required to achieve this effect.

- Microbiological data may be needed to supplement the safety assessment of the antimicrobial food additive under section 409(c)(3)(A) of the Act, which states that "... [n]o such regulation shall issue if a fair evaluation of the data before the Secretary fails to establish that the proposed use of the food additive, under the conditions of use to be specified in the regulation, will be safe..." Cases where microbiological data may be used to supplement the safety assessment are described in Items I, L, and M below.

E. How do I get my antimicrobial food additive approved?

Antimicrobial food additives are regulated through the FAP process, the FCN process, or the TOR exemption process. Section 409(b) of the Act sets forth the statutory requirements for data in an FAP to establish the safety of a food additive; section 409(h) sets forth the requirements for notification of a food contact substance; and 21 CFR 170.39 sets forth the requirements for a TOR submission. A more detailed description of the information to be submitted in an FAP and the proper format are specified in 21 CFR 171.1; information requirements for a food contact notification are found in 21 CFR 170.101. Guidance documents from the FDA detailing the procedures for preparing and submitting an FAP, FCN, or TOR submission can be found on the CFSAN Internet.

It is important to note that there are some antimicrobial additives for which the proposed use makes them both a food additive and drug (e.g., a no-rinse hand sanitizer used by food handlers). In this case, the product will have to comply with the requirements of the Act applicable to both food additives and drug products.

F. Why does FDA require that data on the intended effect of an antimicrobial food additive be included as part of the submission seeking approval of the additive?

Section 409(b)(2)(C) of the Act requires that a petition for a food additive contain all relevant data bearing on the physical or other technical effect such additive is intended to produce, and the quantity of such additive required to produce such effect. Therefore, data on the intended effect are required in a petition for an antimicrobial food additive. Furthermore, if FDA determines that a tolerance is needed to ensure that the petitioned use of an antimicrobial food additive will be safe, intended effect data will be used to ensure that the tolerance is set at a level no higher than what is reasonably required to achieve the intended physical or other technical effect. In addition, if a tolerance is necessary and data do not establish that the petitioned use will accomplish the intended physical or other technical effect, FDA is not authorized to establish a regulation for that use (section 409(c)(4) of the Act).

For antimicrobial food additives used on meat or poultry, FDA and FSIS have separate regulatory responsibilities which must be satisfied before the additive may be legally marketed. For these cases, intended effect data will be needed to satisfy the requirements of both FDA and FSIS. Under the Federal Meat Inspection Act (FMIA) and the Poultry Products Inspection Act (PPIA), FSIS has authority over suitability of food ingredients and sources of radiation used in meat and poultry processing plants.

In accordance with the procedures described in the MOU between FDA and FSIS, requests for approval to use food ingredients and sources of radiation in the production of meat and poultry products are evaluated simultaneously for safety by FDA and for suitability by FSIS. Prior to submission, petitioners and notifiers may wish to consult with FSIS independently; however, FDA believes joint consultations with FDA and FSIS facilitate the petition and notification processes.

G. What types of data and other information should be included to demonstrate that the use of an antimicrobial food additive achieves its intended physical or other technical effect?

To demonstrate that an antimicrobial agent achieves its intended technical effect and that the proposed use level is the minimum level necessary to accomplish the intended technical effect, the following information is recommended at a minimum:

- The chemical identity or biological identity of the antimicrobial agent, which ever is appropriate;
- A detailed description of intended antimicrobial effect and identification of any individual or groups of targeted microbes, if appropriate;
- A description of the conditions of use and any limitations on conditions of use, e.g.:
 - types of foods;
 - proposed use level or range;
 - temperature range of use;
 - method of application, such as spraying, dipping or fumigating, when applicable;
 - post-processing steps (e.g., potable water rinse, cooking by the consumer);
- Antimicrobial effect data, including full reports of the efficacy studies;
- Directions, recommendations, and suggestions regarding the proposed use, as well as a sample of the label proposed for the food additive and any labeling that will be required on the finished food as a result of the use of the food additive; and
- For a petition, proposed wording for establishing or amending a food additive regulation is recommended. This draft regulation helps FDA understand the petitioner's intent and may help the petitioner understand the issues that need to be addressed.

H. How should a study be designed to demonstrate the antimicrobial food additive's effect?

FDA recommends that any study carried out to support the intended technical effect of an antimicrobial food additive should be designed to generate data that directly supports any particular effect(s) specified. For example, if the intended technical effect is extending shelf life, the study should generate data which measure shelf life; or if the intended technical effect is the control of specific organisms, the study should generate data which directly enumerate those organisms. FDA recommends that any of the subject studies reflect the following characteristics, to the extent practical:

- The study is conducted in a manner that simulates, to the extent feasible, the intended conditions of use of the antimicrobial food additive;
- The study is conducted using samples of the relevant medium (e.g., food, process water, food packaging) treated under the proposed conditions of use, and the study includes appropriate controls;
- The study focuses on pertinent organisms that the antimicrobial food additive is intended to target, especially those associated with a given medium (e.g., Salmonellas and *Campylobacter jejuni* for poultry, *E. coli* for beef, *Vibrio* spp. for seafood, Salmonellas for juices, etc.);
- Where appropriate, a study uses a direct method for enumeration of microorganisms such as plate counting or visual microscopic counts, as opposed to measuring biomass, and evaluates the reduction (or suppression) of microorganisms affected by the treatment;
- Enumeration methods capture damaged or stressed microbial cells that survive the antimicrobial treatment;
- The study includes collection and analysis of replicate samples for each data point with a description of the variability of the data; and
- When appropriate, the study includes an analysis of the data such as a comparison of the treatment and control.

A petition or notification will not be treated differently simply because an alternative approach was chosen. FDA invites submitters to consult with the agency in designing experimental protocols and recommends that submitters provide their experimental protocol to the agency for comment prior to the initiation of any study. It is the agency's experience that these consultations lead to consensus between the agency and the submitter prior to experimentation being conducted. FDA believes these consultations result in studies that are more likely to address the agency's concerns which leads to a more efficient regulatory process and a faster time to market for the proposed food additive.

I. Are there unique circumstances that should be taken into consideration when designing a study to show that an antimicrobial food additive achieves its intended effect?

There are a number of unique circumstances that might be considered when designing a study to show an antimicrobial food additive's effect. Several are described below.

- A study should consider the typical organisms expected to be observed under the conditions under which they would be present. For example, the commonly consumed portions of beef, lamb, pork, and poultry are generally considered uncontaminated with pathogens prior to slaughter. Contamination with enteric pathogens may occur as a result of improper slaughtering techniques and subsequent processing. Therefore, we believe that enteric pathogens are the likely organisms of concern for meat and poultry, and they should be the subject of any intended effect studies. (**NOTE:** We recommend that FSIS be consulted regarding the design of any study where the intended use includes the treatment of meat and poultry.)
- Seafood, fruits and vegetables may have indigenous pathogens present at harvest, or

(different) pathogens may be introduced during harvest or processing. We recommend that petitioners/notifiers consider whether their additive is equally effective against indigenous and introduced microorganisms.

- Experimental design should consider and address whether the use of the antimicrobial agent may result in unintended consequences. For example, an antimicrobial agent may change the microbiological profile of food such that it suppresses one group of pathogenic microorganisms while allowing others to proliferate, thereby creating a potential health problem.
- Organoleptic changes affected by spoilage organisms are indicators that consumers may use to gauge the freshness of meat and poultry, seafood, and produce, and indirectly, their safety. As such, an antimicrobial agent that preferentially eliminates spoilage organisms over pathogens might allow the pathogens to proliferate while suppressing spoilage organisms and their effects. Under such conditions, a consumer's senses may not reliably discern spoiled and contaminated products, and the use of an antimicrobial agent under those conditions might not be safe. We recommend submitters provide data on the effects of their agent on specific pathogens as well as general (spoilage) populations for comparison; typically, aerobic plate counts are sufficient to characterize general populations.

J. Does FDA recommend any specific experimental methods?

FDA recognizes it is impractical to design a standard experimental protocol that addresses all relevant safety issues for every antimicrobial agent. However, there are a number of resources specific to microbiological methods that the agency recommends. FDA publishes an online version of its Bacteriological Analytical Manual which presents useful laboratory procedures for microbiological analyses of foods and cosmetics. Furthermore, FDA maintains a website with numerous links to related resources on [Microbiological Methods](#). Also, FSIS maintains a Microbiology Laboratory Guidebook of current protocols for analytical tests required by FSIS in its regulatory activities on meat, poultry and egg products; these test procedures may be useful in the experimental design of technical effect studies. However, a petition or notification will not be treated differently simply because an alternative study design was chosen.

K. What is FDA's performance standard for a new antimicrobial food additive?

A performance standard defines the minimal level of reduction of microorganisms from the use of the antimicrobial food additive (e.g., a 5-log reduction in the number of microbe(s) targeted). Given the variability in the intended technical effect of antimicrobial food additives and types of food treated, FDA does not have a single performance standard for antimicrobial food additives. However, to prove that an additive achieves its intended technical effect as an antimicrobial agent, data from an efficacy study should demonstrate that, at a minimum, there is a measurable difference between the treated samples and a negative control (e.g., the treatment absent the active agent). Such a demonstration may be achieved through statistical analysis, graphical comparison, or another equivalent method. In those particular cases where the intended technical effect specifies the use of the additive as part of a process where a performance standard has been established by regulation (e.g., Juice HACCP (21 CFR 120.24)) or regulatory guidance (e.g., FSIS guidance on control of *Listeria monocytogenes*), FDA may consider that performance standard when regulating the additive.

L. What information may be helpful to provide to FDA to demonstrate the intended technical effect of a source of radiation as an antimicrobial treatment for food?

A source of radiation used to treat food is included in the food additive definition (section 201 (s) of the Act). Furthermore, section 402(a)(7) of the Act states that a food is adulterated if it has been subjected to radiation, unless the use of the regulation was in conformity with a regulation or exemption under section 409 of the Act. Because a source of radiation used to treat food does not meet the definition of a food contact substance in that it has a technical effect in the food, it is regulated through the FAP process under section 409 rather than the FCN process or the TOR exemption process. In addition to information typically submitted in an FAP, a petition for the use of a source of radiation as an antimicrobial treatment for food should include information related to technical effect, such as:

1. Information describing the microbiological profile of targeted foods (occurrence and levels of pathogenic and non-pathogenic microorganisms); and
2. Information describing the effects of the proposed irradiation on microorganisms in or on the targeted food, including growth patterns of surviving microorganisms compared with food that has not been irradiated. For example, *Clostridium botulinum* is of particular concern as a potential microorganism surviving irradiation. Therefore, it may be necessary to consider whether *C. botulinum* is able to proliferate to a greater extent in food treated by irradiation than in untreated food because of a reduced number of competing spoilage organisms.

M. What additional safety information may be helpful to provide to FDA if my antimicrobial food additive is derived from a microorganism?

If an antimicrobial food additive is derived from a microorganism, FDA recommends that the following additional information be provided, at a minimum:

1. The biological identity of the specific isolate of microorganism to be used for production. If the strain has been genetically manipulated, a description of how the strain was derived, including information about any strain contributing genetic material to the production strain should be included with the submission;
2. A description of the procedures used to maintain the cultural purity and genetic stability of the production microorganism. Details of procedures employed to assure strain purity and integrity should be included with the submission;
3. A description of the quality control procedures used during production, the procedures for assurance of cultural purity, and the procedures to be followed if contamination is observed in the starter (pure) cultures or during production;
4. A description of the methods used to verify the absence of clinically relevant antibiotics. Antibiotics approved by FDA for pharmaceutical uses should not be produced during the manufacture of the antimicrobial agent;
5. Information that demonstrates that the production strain is not infectious or toxicogenic, and that no toxin is present at toxicologically significant levels in the preparation for use in food, if it is necessary to employ a toxicogenic strain; and

6. A description of the methods employed and relevant quality control procedures followed to ensure that no viable cells of the production strain are found in the product when those cells represent a safety concern.

FDA understands that there may be newly developed antimicrobial products for which some of these recommendations may not be valid. A petition or notification will not be treated differently simply because safety information other than that recommended here was provided.

We will consider the sufficiency of the safety information provided with antimicrobial product petitions on a case-by-case basis.

[1] This guidance has been prepared by the Office of Food Additive Safety in the Center for Food Safety and Applied Nutrition at the U.S. Food and Drug Administration.

[2] *Guidance on the Procedures for Joint Food Safety and Inspection Service (FSIS) and Food and Drug Administration (FDA), Approval of Ingredients and Sources of Radiation Used in the Production of Meat and Poultry Products*, U.S. Department of Agriculture, Docket No. 00-022N, *E. coli* O157:H7 Contamination of Beef Products.

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