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# **Best Practices for Convening a GRAS**

## **Panel:**

## **Guidance for Industry**

### ***Draft Guidance***

**This guidance is being distributed for comment purposes only.**

Although you can comment on any guidance at any time (see 21 CFR 10.115(g)(5)), to ensure that the Agency considers your comment on this draft guidance before it begins work on the final version of the guidance, submit either electronic or written comments on the draft guidance within 180 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments to <https://www.regulations.gov>. Submit written comments to the Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number FDA-2017-D-0085 listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document as it relates to substances used in human food, contact the Center for Food Safety and Applied Nutrition (CFSAN) at 240-402-1200.

For questions regarding this draft document as it relates to substances used in animal food, contact the Center for Veterinary Medicine (CVM) at 240-402-5838.

**U.S. Department of Health and Human Services  
Food and Drug Administration  
Center for Food Safety and Applied Nutrition  
Center for Veterinary Medicine**

**November 2017**

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**Written GRAS panel policy** – A written policy to govern procedures for assembling and managing a GRAS panel, including an assessment of the potential for bias created by a conflict of interest or an appearance issue in an individual under consideration for selection as a member of a GRAS panel and including strategies for managing conflicts and appearance issues.

## **V. Recommendations**

### **A. Introduction**

Convening a GRAS panel and relying on the GRAS panel as a proxy for the larger scientific community knowledgeable about the safety of substances directly or indirectly added to food is one mechanism that proponents have used to support a proponent's conclusion that the safety of a substance under the conditions of its intended use in human food or animal food is generally recognized. However, the use of a GRAS panel is not the only mechanism for doing so, and the use of a GRAS panel does not necessarily mean that the GRAS criteria have been met. As discussed in section II.A, we have established criteria for eligibility for classification as GRAS in 21 CFR 170.30 and 21 CFR 570.30 for substances intended for use in human food and animal food, respectively.

In the remainder of the recommendations section of this draft guidance, we discuss detailed recommendations related to selecting GRAS Panel members, the operation of a GRAS panel, submitting a GRAS notice to FDA, and other recommendations as summarized immediately below.

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#### *1. Recommendations Related to Selecting GRAS Panel Members*

To convene a GRAS panel that can effectively evaluate the available scientific data, information, and methods and act as a proxy for the larger scientific community of qualified experts, and to reduce the risk that bias (or the appearance of bias) will affect the credibility of the GRAS panel report, as discussed in more detail in sections V.B through V.D, we recommend that the proponent or organizer establish and implement a written GRAS panel policy to:

- Assess and balance the knowledge, experience, and perspectives of potential GRAS panel members in terms of the subtleties and complexities of the particular scientific and technical issues applicable to the food substance and its intended use in human food or animal food;
- Consider and take steps to address procedural issues associated with the organization and deliberations of the GRAS panel;
- Consider and take steps to assess potential GRAS panel members for conflicts of interest and appearance issues;
- Document how the proponent or organizer applied the written GRAS panel policy to the selection and vetting of each member of the GRAS panel; and

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B. Appropriate and Balanced Expertise in a GRAS Panel

1. General Considerations When Convening a GRAS Panel

We recommend that the organizer, the proponent’s attorney or agent, or employees of the proponent, organizer, or the proponent’s attorney or agent not be members of a GRAS panel, because such individuals could have a predictable financial interest in the GRAS panel’s decision. Such individuals could have a conflict of interest in that they could be helpful to a GRAS panel in that an individual could act in a way that is not in the best interest of the GRAS panel or the proponent or organization. The GRAS panel without providing an opinion that would be included in any report generated by the GRAS panel; such participation would be analogous to “non-voting members” who are granted a waiver when necessary to afford essential expertise to an FDA advisory committee (Ref. 19).

**1.7.2 John R. Endres, ND—Panel Member**  
Dr. Endres is the chief scientific officer for AIBMR Life Sciences, Inc. in Seattle, Washington since 2006. Dr. Endres earned a degree in naturopathic medicine at the University of Western States.

**1.7.3 Amy Clewell, ND, DABT—Panel Member**  
Dr. Amy Clewell is the Vice President of Scientific and Regulatory Affairs at AIBMR Life Sciences. Dr. Clewell earned a Bachelor of Science degree in biology from the University of Washington.

2. Appropriate Expertise in a GRAS Panel

We recommend that either the proponent of the food substance, or an organizer who acts on behalf of the proponent, consider individuals with expertise that reflects the physical, chemical, and biological properties of the food substance and the scientific questions that arise in relation to the conditions of its intended use. At a minimum, we recommend that a GRAS panel include members with expertise in chemistry or biochemistry, toxicology, and exposure assessment, because our experience with GRAS notices demonstrates that these scientific disciplines broadly apply to most safety evaluations. For substances intended for use in animal food, a GRAS panel should include members with expertise to evaluate the safety of the substance under the conditions of its intended use, including the safety of the substance under the conditions of its intended use in producing animals, for humans consuming human food(s) derived from these animals. See Table 1 for examples of additional recommended expertise on a GRAS panel based on the food substance and/or the conditions of its intended use.

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Table 1.—Examples of Recommended Expertise on a GRAS Panel Based on the Food Substance or the Conditions of its Intended Use

Food Substance or Conditions of its Intended Use	Recommended Expertise
Enzyme produced from a microorganism	Microbiology; enzymology
Botanically-derived substance	Plant chemistry
Substance that could have allergenic properties	Allergy
Use in infant formula	Pediatric nutrition
Substance that has a specific physiologic effect	Expertise to address the long-term significance of the physiological effect in the general population or in relevant subpopulations
Complex ingredient, or ingredient defined partly by its method of manufacture	Chemistry; food manufacturing; food processing
Microbial ingredient	Microbiology; immunology
Substance intended to supply a nutrient	Nutrition

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<b>Food Substance or Conditions of its Intended Use</b>	<b>Recommended Expertise</b>
Substance intended for a technical effect (e.g., emulsifier, binder)	Chemistry; food manufacturing; food processing

In some cases, the proponent is evaluating the safety of a substance that is already used in food because, for example, there has been a significant change in the manufacturing process; there would be an increased level of the substance compared to the levels already in use; or the intended use of the substance would be different from existing uses. If a proponent decides to convene a GRAS panel in such circumstances, the emphasis in selecting members of a GRAS panel should be on the expertise necessary to assess the change. For example, if there has been a significant change in the manufacturing process, a chemist, biochemist, or food technologist should evaluate the potential for toxic contaminants or impurities associated with the new process, and a toxicologist or other scientist with expertise applicable to the nature of those contaminants or impurities should evaluate the safety of the substance produced using the new manufacturing process. For increased use levels, the key expertise would be toxicology or a related scientific discipline to evaluate whether the available data and information support the safety of an increased exposure to the substance. If the intended use of the substance would be significantly different from existing uses, an individual with expertise in exposure assessment should evaluate the new estimated dietary exposure and one or more individuals with expertise in the potential toxicological or physiological effects of the substance under the new conditions of use should evaluate whether the available data and information support the safety of the substance under the new conditions of use. In the case of a substance intended for use in animal food, for example, if the intended use of the substance would be for different animal species, an individual with expertise in assessing safety for the target animal, and potentially for human food(s) derived from the target animal, should evaluate animal and human exposures and possible toxicological and physiological effects of the substance under the new conditions of use.

To optimize the applicable experience of the GRAS panel members, in general we recommend that a proponent or organizer who convenes a GRAS panel convene an ad hoc GRAS panel rather than a standing GRAS panel. However, a standing GRAS panel could be appropriate when considering a class of substances closely related by conditions of use, function, or other properties, where the experience and expertise of the panel members align with the scientific questions applicable to that class of substances, or if a standing GRAS panel is supplemented with members with additional expertise to address the physical, chemical, and biological properties of a specific food substance and the complexity of the scientific questions that arise in relation to the conditions of its intended use.

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#### 3. *Number of Members of a GRAS Panel*

We recommend that the proponent or organizer determine the total number of GRAS panel members, as well as the number of GRAS panel members with the same expertise, based on the substance, the complexity of the scientific issues associated with the conditions of its intended use, and the available data and information about the substance. For example, when the available data and information relevant to the intended conditions of use of the substance raise no safety questions that experts would need to interpret and resolve, a single representative of each

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applicable expertise could suffice. However, when a GRAS panel contains a single expert of each applicable scientific discipline, there would be no means for the GRAS panel as a whole to resolve questions raised by one panel member about the safety of the substance under the conditions of its intended use in light of certain data and information relevant to that panel member's scientific expertise.

When the available data and information relevant to the intended conditions of use of the substance involve complex scientific issues that experts would need to interpret and resolve, we recommend that the proponent or organizer consider having multiple representatives with expertise applicable to those scientific issues so that there can be genuine discussion and critical analysis on those complex scientific issues.

Importantly, although there is general recognition that the use of a GRAS panel regarding the safety of a substance, when available data and information are limited and scientific community expertise in a particular scientific discipline. Instead, the GRAS panel report would more appropriately be a resource for the proponent to use in identifying data gaps and information about ongoing scientific debate and dispute.

3	GRAS	2	Non-Voting
	1.7.1 Judith Hauswirth PhD—Panel Chair		
	1.7.3 Amy Clewell, ND, DABT—Panel Member		
	1.7.2 John R. Endres, ND—Panel Member		
	1.7.4 Vickie Modica, ND—Panel Member (Non-Voting)		
	1.7.5 Maureen Dunn, ND—Panel Member (Non-Voting)		

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### **C. Assessment and Management of Procedural Issues Associated with the Organization and Deliberations of a GRAS Panel**

We recommend that a written GRAS panel policy address the potential for bias that could occur through procedures associated with the organization and deliberations of a GRAS panel by:

- Establishing clear roles and responsibilities for each member of the GRAS panel;
- Establishing clear decision-making procedures that the GRAS panel will follow;
- Specifying whether the charge to the GRAS panel will inform the members of the GRAS panel about the potential for bias (e.g., due to cognitive patterns); and
- Considering factors such as seniority or perceived status among panel members and the leadership skills of an individual who would be the formal leader of the GRAS panel (or likely to become the informal leader if the proponent or organizer does not appoint a formal leader).

We also recommend that the proponent take appropriate steps to avoid influencing the deliberations of the GRAS panel – e.g., by formulating the charge to the panel in neutral, unbiased language; limiting communication with the GRAS panel to the minimum necessary to manage the affairs of the GRAS panel efficiently and effectively; and then awaiting the outcome.



**AIBMR Life Sciences, Inc.**

*Natural and Medicinal Products Research*

## **GRAS Dossier:**

# **The Independent Conclusion that the Intended Use of 11 Individual Lactic Acid Bacterial Strains Are Generally Recognized as Safe (GRAS)**

### **Independent Conclusion of GRAS Status By:**

Ildong Bioscience Co., Ltd.

17 Poseunggongdan-ro, Poseung-eup, Pyeongtaek-si  
Gyeonggi-do, 17957, Republic of Korea

### **Prepared by:**

AIBMR Life Sciences, Inc.

1425 Broadway, Suite 458  
Seattle, WA 98122

**December 2, 2020**



## A. Expert Evaluation

Ildong Bioscience Co., Ltd. (hereafter referred to as ‘ILDONG’), the proponent of this GRAS conclusion, engaged AIBMR Life Sciences, Inc. to convene a Panel of experts (“GRAS Panel”) who are qualified by training and experience to evaluate the safety of food ingredients for the purpose of evaluating whether the available scientific data, information, and methods establish that ILDONG’s 11 individual non-genetically modified lactic acid bacterial strains are safe under their intended conditions of use in food. The GRAS Panel report is attached as Exhibit 1. The appendices to the GRAS Panel report are included in the GRAS dossier as Exhibit 3.

## B. Responsible Individual and Principal Address

Sarah Park  
Assistant Manager  
Ildong Bioscience Co., Ltd.  
17 Poseunggongdan-ro, Poseung-eup, Pyeongtaek-si  
Gyeonggi-do, 17957, Republic of Korea  
+82(0)70 52088310  
sarah@ildong.com

11 GRAS  
GRAS Panel

## C. Name of the Substances

The 11 individual non-genetically modified lactic acid bacterial strains that are the subject of this GRAS conclusion are listed below:

ILDONG Strain	Taxonomic Name
<i>Bacillus coagulans</i> IDCC 1201	<i>Bacillus coagulans</i>
<i>Bifidobacterium breve</i> IDCC 4401	<i>Bifidobacterium breve</i>
<i>Bifidobacterium lactis</i> IDCC 4301	<i>Bifidobacterium animalis</i> subsp. <i>lactis</i>
<i>Lactobacillus acidophilus</i> IDCC 3302	<i>Lactobacillus acidophilus</i>
<i>Lactobacillus casei</i> IDCC 3451	<i>Lactobacillus casei</i> subsp. <i>casei</i>
<i>Lactobacillus johnsonii</i> IDCC 9203	<i>Lactobacillus johnsonii</i>
<i>Lactobacillus plantarum</i> IDCC 3501	<i>Lactobacillus plantarum</i>
<i>Lactobacillus reuteri</i> IDCC 3701	<i>Lactobacillus reuteri</i>
<i>Lactobacillus rhamnosus</i> IDCC 3201	<i>Lactobacillus rhamnosus</i>
<i>Lactococcus lactis</i> IDCC 2301	<i>Lactococcus lactis</i>
<i>Streptococcus thermophilus</i> IDCC 2201	<i>Streptococcus thermophilus</i>

Abbreviation: IDCC, ILDONG Culture Collection



## Conclusion of the GRAS Panel

The GRAS Panel has, independently and collectively, critically evaluated this safety assessment of ILDONG's 11 non-genetically modified lactic acid bacterial strains and unanimously opine that the scientific data, information, and methods herein described establish that these strains, produced in accordance with Good Manufacturing Practice and meeting the specifications presented in the document, are reasonably certain to be safe under the conditions of their intended use as food ingredients. In addition, the GRAS Panel believes that other experts qualified by training and experience to evaluate the safety of food ingredients would concur with this opinion.

**Panel Members:**

**Date:**



December 2, 2020

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Judith Hauswirth, PhD  
Chair of Expert Panel



December 2, 2020

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John R. Endres, ND  
Panel Member



December 2, 2020

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Amy Clewell, ND, DABT  
Panel Member

## 1.7 Biosketches of the GRAS Panel

### 1.7.1 Judith Hauswirth PhD—Panel Chair

Dr. Hauswirth has a PhD in biochemistry from Oregon State University, Corvallis, Oregon 1969 and a BS in chemistry, University of California, Davis, California, 1965. She also received a National Institutes of Health postdoctoral fellowship in pharmacology at Yale University, New Haven, Connecticut and a National Cancer



Institute Career Development Award and research grant. She is currently the sole proprietor of her own consulting firm where she provides expert consultation to private clients on toxicology issues related to toxicity testing, risk assessment, and hazard evaluation. She also provides regulatory advice, serves as an expert in data compensation cases, evaluates laboratory reports, and assists in designing atypical toxicology studies and monitors toxicology studies of all types. She has served as an expert on GRAS conclusion panels and made presentation to the EPA Human Science Review Board and the Scientific Advisory Panel. She has over 38 years of experience in toxicology, biochemistry, and drug metabolism, including basic research and regulatory toxicology.

She is a member of the American Chemistry Society and a past member of the American College of Toxicology, the New York Academy of Sciences, and the Association of Government Toxicologists. She was councilor for the American College of Toxicology from 1997 to 2000. She was, also, an advisor to the National Academy of Sciences Committee on Pesticides in the Diets of Infants and Children. She received the Food and Drug Commendable Service Award for management and quality of output, the FDA Group Recognition Award as a member of the Nitrofurantoin Hearing Team, the EPA Bronze Medal for Commendable Service for formulation of the inerts policy, and the EPA Bronze Medal for Commendable Service for performance on the Toxicology Branch Peer Review Committee.

She has worked for several consulting firms as a toxicologist, including van Gemert and Hauswirth, LLC, Charles, Conn, and van Gemert, LLC, ChemReg International, LLC, and Jellinek, Schwartz, and Connolly where she became the Vice President of Toxicology and Chemistry. Prior to her consulting career, she was a Branch Chief at the Environmental Protection Agency in the Office of Pesticides Program, Health Effects Division and acted as Director of the Division of Drugs and Environmental Toxicology at the Food and Drug Administration. While at FDA, she was part of the Center for Veterinary Medicine and the Bureau of Foods and did basic research in the area of genotoxicity and mutagenicity as well as her roles as manager and expert in toxicology testing and regulation of food animal drugs. At the Biochemistry Research Division of Sinai Hospital of Baltimore, where she became the assistant director, she conducted basic research on the role of nutrition in the metabolism of carcinogens. She has published book chapters in the areas of plant biochemistry, vitamin E, and pesticide toxicology. She has published in journals such as Cancer Research, Archives of Biochemistry and Biophysics, and Environmental Mutagens.

#### **1.7.2 John R. Endres, ND—Panel Member**

Dr. Endres is the chief scientific officer for AIBMR Life Sciences, Inc. in Seattle, Washington since 2006. Dr. Endres earned a degree in naturopathic medicine at

Bastyr University in Kenmore, Washington in 2004 and is licensed by Washington State Department of Health as a physician. He is a full member of the Society of Toxicology (SOT). Dr. Endres has been a member of numerous expert panels assembled for the evaluation of GRAS independent conclusions. He meets frequently with FDA Office of Food Additive Safety (OFAS) in College Park, MD for GRAS pre-submission meetings. Dr. Endres has been a contributing author on many safety assessments published in academic journals specializing in toxicology. He is the monitoring scientist for AIBMR toxicology studies designed to study the safety of oral consumption of ingredients to be added to foods and dietary supplements. Dr. Endres is on the Editorial Advisory Boards for Nutritional Outlook and is on the Executive Advisory Board for Vitafoods Europe. He has also been one of 33 voting members on the NSF International Joint Committee to develop Publicly Available Standards (PAS) for GRAS on behalf of the Grocery Manufacturers Association (GMA). At AIBMR, he manages a team of scientific and regulatory consultants specializing in the natural products and functional foods industries.

Prior to his work at AIBMR, Dr. Endres was involved in cancer research conducted at the Bastyr University Research Institute (BURI) and Fred Hutchinson Cancer Research Center, both located in Seattle, Washington. He screened botanical extracts for their inhibitory effect on the growth of various cancer cell lines. He has also been the recipient of grants to present research in the United Kingdom at Westminster University, Middlesex University, and Oxford Natural Products. He has presented research at various venues, including American Medical Association sponsored conferences where, in 2001, he received an Award of Excellence in Research. Dr. Endres was a teaching assistant in laboratory chemistry and a research assistant in natural products research, with a focus on production, purification, and analytical chemistry of whole plant extracts while attending Bastyr University.

### **1.7.3 Amy Clewell, ND, DABT—Panel Member**

Dr. Amy Clewell is the Vice President of Scientific and Regulatory Affairs at AIBMR Life Sciences. Dr. Clewell earned a Bachelor of Science degree in biology from Indiana University in Bloomington, Indiana and a doctoral degree in Naturopathic Medicine from Bastyr University in Kenmore, Washington. She maintains her physician's license in the State of Washington. She is a diplomat of the American Board of Toxicology, a full member of the Society of Toxicology (SOT) and has been a member of numerous expert panels assembled for the evaluation of GRAS independent conclusions. Dr. Clewell is an author on many peer-reviewed journal publications, especially related to the toxicological evaluation of food ingredients. Her authorship also includes book chapters and trade articles. She has over 12 years of experience in natural products regulatory consulting and specializes in the preparation of GRAS independent conclusion dossiers, as well as FDA GRAS notices and New Dietary Ingredient (NDI)

**notifications.** She is also involved in the evaluation and compilation of scientific research on the efficacy of ingredients and regulatory compliance for natural products. She plays a strong role in the management of projects at AIBMR Life Sciences.

In addition to work at AIBMR, Dr. Clewell has clinical experience as a licensed physician in Washington State, as well as extensive research experience. Her work in research began as a student and laboratory technician as an undergraduate at Indiana University where she spent three years working in the area of translational initiation using *Saccharomyces cerevisiae* as a model system. She continued her research pursuits for another five years as a research technician and laboratory manager in Dr. Karla Kirkegaard's laboratories at both the University of Colorado and Stanford University, studying the biochemistry of polio and hepatitis C virus propagation using an *S. cerevisiae* model. She remained active in research in various capacities while attending Bastyr University for her doctorate. She is the past-president of the Indiana Association of Naturopathic Physicians and a current member of the American Association of Naturopathic Physicians.

#### **1.7.4 Vickie Modica, ND—Panel Member (Non-Voting)**

Vickie Modica, ND, is a Scientific and Regulatory Consultant at AIBMR. Dr. Modica earned her doctorate in Naturopathic Medicine in 2012 from Bastyr University in Seattle, Washington. Since then, she has cared for patients with chronic illnesses concentrating on diabetes, cardiovascular disease, and cancer. She has worked in both the Seattle area and in Ann Arbor, Michigan.

She earned a Bachelor of Science degree in Cellular and Molecular Biology from the University of Michigan in Ann Arbor. She received a high honors degree based on her undergraduate work in a basic science developmental neurobiology lab. After her research work and before attending Bastyr, she worked in the business sector at multiple high-tech and medical device companies as a consultant and business analyst.

#### **1.7.5 Maureen Dunn, ND—Panel Member (Non-Voting)**

Maureen Dunn, ND, is a Scientific and Regulatory Consultant at AIBMR. Dr. Dunn earned her doctorate in Naturopathic Medicine in 2012 from Bastyr University in Kenmore, Washington. She has provided acute and chronic Naturopathic health care in both Vermont and North Carolina.

Further, she created a virtual integrative health company offering Naturopathic health programs to individuals and groups to the general public. These programs included education, coaching and recommendations on diet, lifestyle and nutraceuticals for people with chronic diseases. She earned a Bachelor of Art degree

in Environmental Studies from Mount Holyoke College in South Hadley, Massachusetts. She also received a Master's in Public Affairs specializing in environmental policy from the University of Washington Evans School in Seattle, Washington. While at the Evans School she co-published a paper, "Investments in Global Warming Mitigation: The Case of "Activities Implemented Jointly". Prior to attending Bastyr, she worked as a consultant to the government on local environmental projects.