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GRAS and NDIN: Regulatory Pathways to a Safe Food Supply

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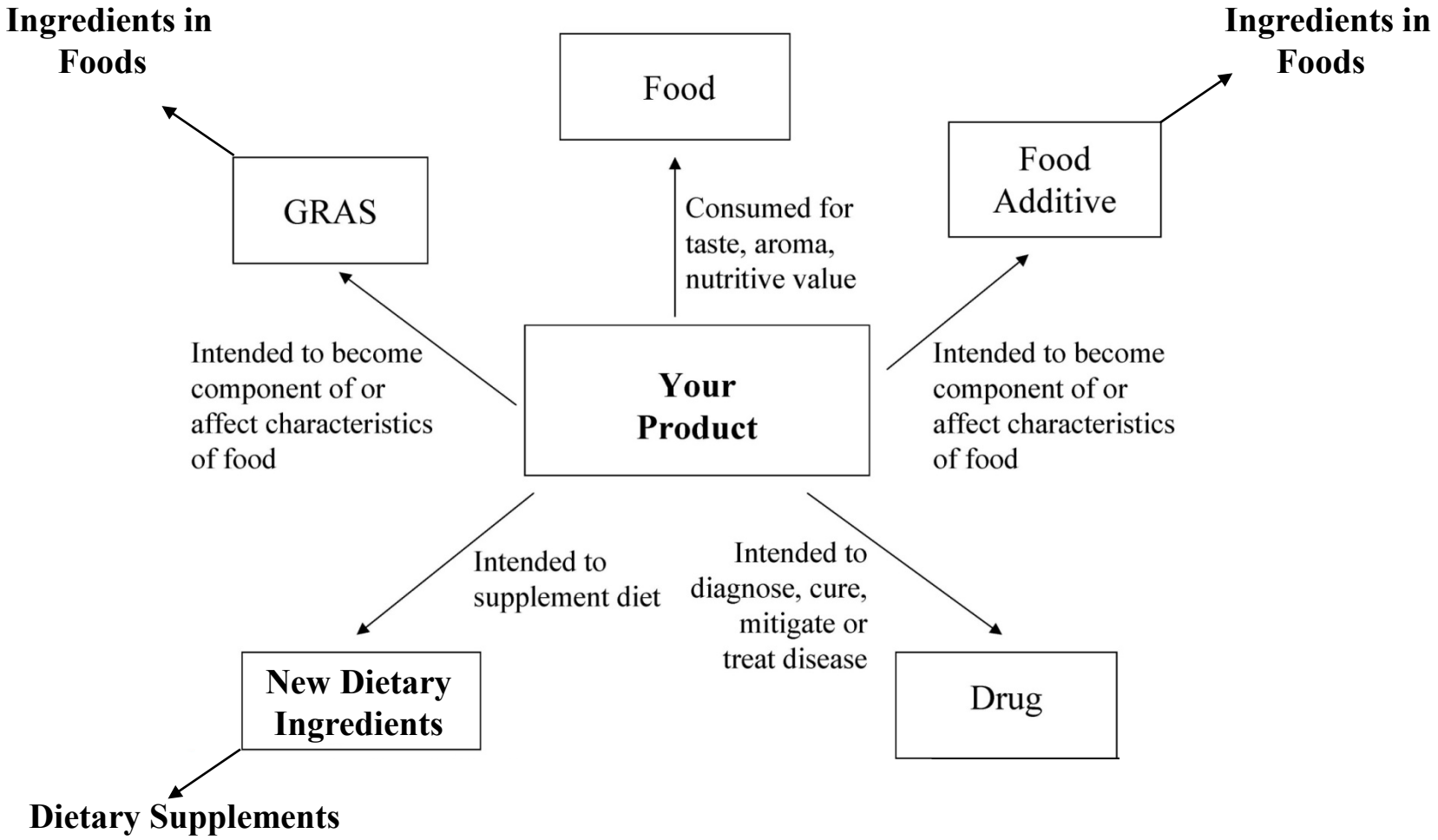
U.S. Regulatory Paths for New Products



GRAS Ingredients

- **Definition (Food Additives Amendment 1958):**
  - General recognition of safety may be based only on the **views of experts qualified by scientific training and experience** to evaluate the safety of substances directly or indirectly added to food
  - Basis may be either scientific procedures or common use in food prior to January 1, 1958
- **GRAS does not require a pre-market approval by FDA**

GRAS Requirements

- **Safety standard is the same as that for food additives, "reasonable certainty of no harm"**
- **Evidence of safety is the same as is required to support approval of a food additive petition**
  - Breadth and quantity of information
  - Quality of information
- **Information must be publicly**
  - Available
  - Accepted
- **May be supported by non-publicly available data**

GRAS Ingredients

- **Determination of GRAS by scientific procedures can use:**
  - **GRAS Panel:** whether a GRAS panel is a sufficient proxy for the larger scientific community depends on a number of factors, such as the subject matter expertise of the members of the GRAS panel and whether the members of the GRAS panel would be considered representative of experts qualified by scientific training and experience to evaluate the safety of the substance under the conditions of its intended use.
  - **GRAS** based on generally available and widely accepted data, information, methods or principles (satisfies the common knowledge and consensus elements) and documentation that the intended uses are determined to be safe through scientific procedures (satisfies the technical element).
  - Notification to FDA is voluntary.

GRAS Expert Panel FDA Guidance

- **Bias**
- **Balance of Expertise**
- **Procedures for Organizing a Scientific Panel and Managing Its Deliberations**
- **Conflict of Interest and Appearance Issues**
- **Information Provided to a GRAS Panel**
- **Documenting the Deliberations and Conclusions of a GRAS panel**
- **Honoraria Provided to Members of a GRAS Panel**

* Best Practices for Convening a GRAS Panel: Guidance for Industry https://www.fda.gov/media/109006/download

Elements of GRAS Determination

- **Signed statements and certifications:** Include statutory basis
- **Description of GRAS Substance:**
  - Physical and chemical characteristics (chemical name, CAS registry number, and chemical structure)
  - Description of the production process
  - Established food-grade specifications (principal components, related substances, impurities and contaminants)
  - Batch analysis results with Analytical Methodology
  - Physical or technical effect

Elements of GRAS Determination

- **Historical Use and Dietary Exposure:** History of use and/or natural occurrence of the GRAS substance in foods; a description of the proposed uses and use levels of the GRAS substance in food. Calculation of estimated daily intake (mean and 90th percentile)
- **Self-Limiting Levels of Use:** May not be applicable
- **Experience Based on Common Use in Food before 1958:** May not be applicable

Elements of GRAS Determination

- **<u>Narrative of the Basis for Conclusion of GRAS</u>:**
  - Evaluation of the safety of consumption of the substance under its intended conditions of use as well as safety of consumption of other components or contaminants (if present)
  - Includes a review of pivotal published and corroborative unpublished studies (*in vitro*, *in vivo* toxicology, ADME and clinical studies in humans)
- **<u>List of supporting data and information</u>**.

Dietary Supplement Including New Dietary Ingredient

Definitions:

- **Dietary Supplement:** product intended to supplement the diet that bears or contains one or more dietary ingredients

- **Dietary Ingredient:** a vitamin, a mineral, an herb or other botanical, an amino acid, a dietary substance for use by man to supplement the diet by increasing the total dietary intake, or, a concentrate, metabolite, constituent, extract or combination of the previous ingredients

New Dietary Ingredient Notification (NDIN)

- **An NDIN is required* for a dietary ingredient not marketed in the United States before October 15, 1994**
  - And was not present in the food supply as an article used for food
  - Changes in the manufacturing process that alter the chemical composition or structure of the old dietary ingredient (ODI)
  - Changes that alter the composition of materials used to make the ODI, such as using a different part of a plant

*Notification required 75 days premarket; however, this is not an FDA premarket approval process (e.g. petition process)

Regulatory Oversight of New Dietary Ingredients

Safety is defined as:

- Will reasonably be expected to be safe under the conditions of use defined in the labeling

NDIN: Elements of Safety Assessment

- **Identity of the NDI including manufacturing, methods, specifications, analytical methods.**
- **The level of the NDI in the dietary supplement.**
- **The conditions of use recommended or suggested in the labeling of the dietary supplement or the ordinary conditions of use of the supplement.**
- **The history of use or other evidence of safety establishing that the dietary ingredient, when used under the conditions recommended or suggested in the labeling of the dietary supplement, will reasonably be expected to be safe.**
  - Comprehensive Safety Profile

NDIN: Elements of Safety Assessment

- **Comprehensive Safety Profile for the NDI**
  - Toxicology Studies (OECD protocol)
  - Human Studies
  - Other Studies
  - History of Use
  - Other Evidence of Safety

A Successful NDIN Depends Upon:

1) it is expected that close to 100% of the product will be characterized or standardized;

2) based on manufacturing process and product characterization, specifications are set to control components that would present a safety concern or that would impact the functionality of the product;

3) once characterization is complete and the product is defined by appropriate specifications, toxicology testing of the product of commerce is initiated if needed.

Manufacturing Process

- **Documentation of the species and plant part used.**
- **Description and flow diagram of the manufacturing process.**
- **Description of the critical control steps involved in maintaining the quality of the finished product.**
- **Certificates of Analysis for all raw materials and processing aids.**
- **cGMP compliance of the production facility.**

Identity of the Finished Product

- **Product specifications.**
- **Batch data from at least three non-consecutive lots showing compliance with the product specifications.**
  - Compositional, quality, and impurity testing (such as pesticide, microbiological and heavy metal testing).
- **Validated analytical methods used in determining batch compliance with the product specifications.**

Toxicology Package

- **A review of publicly available NDIN and the recent guidance from FDA confirm the Agency requirement for a minimum of:**
  - A genotoxicology battery and;
  - 90-day rodent toxicology study (OECD No. 408) for a novel natural product extract as part of the testing package.

The Risk Assessment Process

- Applies to GRAS and NDIN

Terms Defined

- **Hazard**
  - Type of toxicity
- **Risk**
  - Likelihood that the toxicity is expressed under conditions of use
- **Safety**
  - Little or no harm; inverse of risk

The Safety of Food Ingredients is Determined Using Risk Assessments

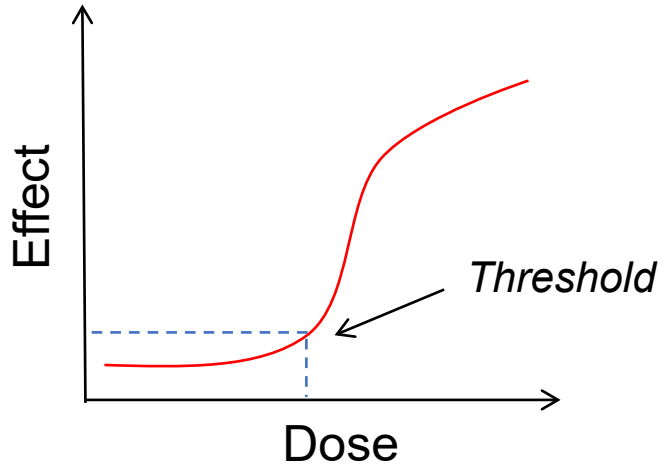
- **Risk assessment = the systematic process of evaluating the potential for adverse effects to hazardous agents or activities**
- **Toxic responses increase in incidence, severity, and sometimes both, as the dose increases**
- **The four elements of a risk assessment:**
  1. Hazard Identification
  2. Hazard Characterization
  3. Exposure Assessment
  4. Risk Characterization

Hazard Identification

- **Is the evaluation of whether a particular chemical can cause an adverse health effect**
- **Involves identifying the potential for exposure, as well as the nature of the adverse effect expected**
- **Methods used to identify hazards:**
  - Computational toxicology studies (i.e., structure-activity relationships)
  - *In vitro* tests
  - Short-term and long-term toxicology studies
  - Human studies (i.e., clinical trials, occupational exposure, epidemiological studies, post-marketing surveillance)

Hazard Characterization

- **Is the quantitative characterization of chemical potency**
- **It is the relationship between exposure and effect.**
  - What is the dose response?
  - Is there a threshold for the toxic effects (NOAEL/LOAEL)?

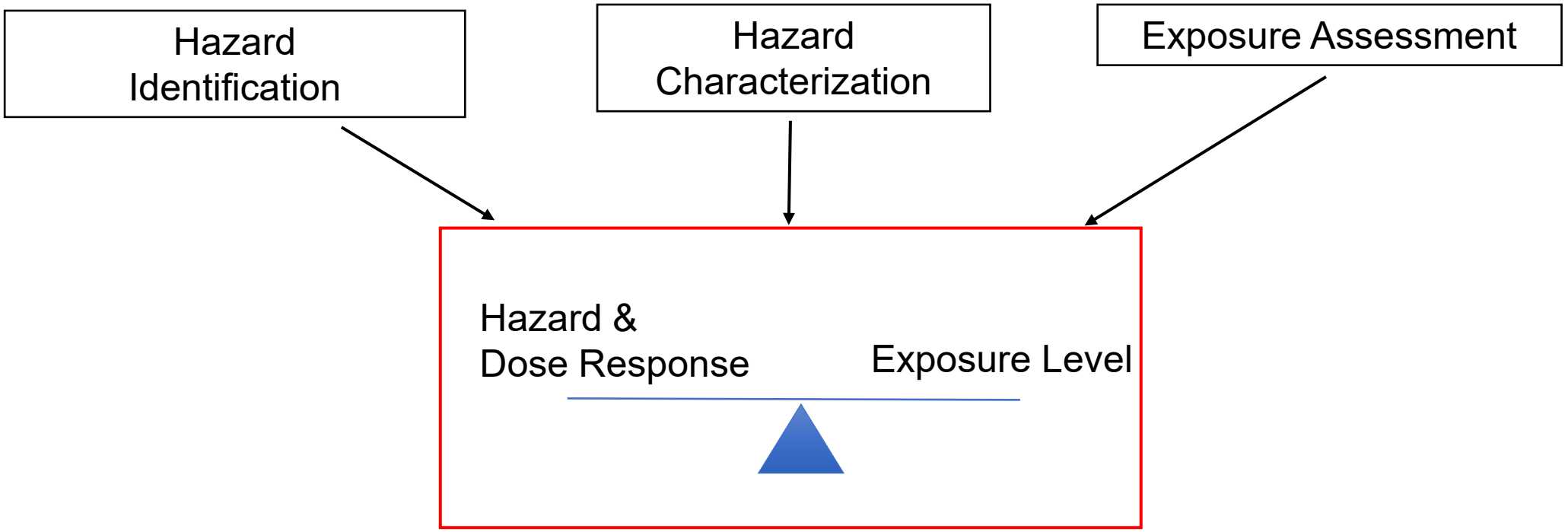


Exposure Assessment

- **Exposure is defined as the concentration or amount of a particular agent that reaches a target organism, system, or (sub)population in a specific frequency for a defined duration (WHO, 2004).**
- **Key elements to assessing exposure:**
  - Dose administered
  - Frequency
  - Duration
  - Route of exposure
  - The amount absorbed/amount reaching target

Risk Characterization

- **Is the quantitative assessment of the likelihood of observing the toxic effect in the population being studied at the exposure level**



Why Transparency in the Risk Process is Critical for Public Acceptance

- **Consumer fear is driven by uncertainty. Uncertainty is introduced when:**
  - Perception that hazards have not been identified.
  - Perception that a hazard has been identified but with no quantification of risk and there is uncertainty in the potential for harm.
  - Perception that bias or conflict of interest has been factored into the conclusion that the product does not present a risk to the public.

In Conclusion: Be Transparent!