



**Impact of Recent Developments and New
FDA Guidance for Food and GRAS
Ingredients on Regulatory Approval**

October 6, 2011

**Claire L. Kruger, Ph.D., D.A.B.T.
A. Wallace Hayes, Ph.D., D.A.B.T.**

6430 Rockledge Drive, Westmoreland Building #503
Bethesda, MD 20817

301-897-2540 • Fax: 301-897-2567

www.spherix.com

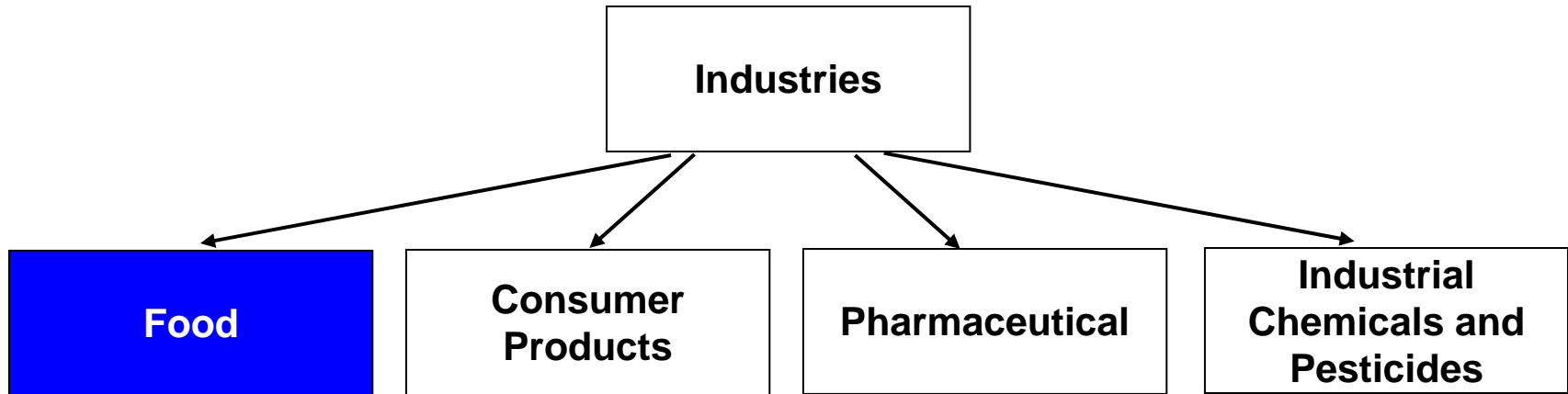
**We provide expert advice
and support throughout the
lifecycle of your products**

- **US Based:**
 - **Claire Kruger, PhD, DABT**
 - **A. Wallace Hayes, PhD, DABT**
 - **Ronald Slesinski, PhD, DABT**
 - **Susan Phillips, MS**
 - **Nancy Booth, PhD**
 - **Yongming Lu, PhD**
 - **Roger Clemens, PhD, CNS**
 - **Dietrich Conze, PhD**
 - **Robert Lodder, PhD**
- **International:**
 - **John Howlett, BSc – EU**
 - **Nino Binns, PhD – EU**
 - **Silvia Berlanga de Moraes Barros, PhD – Latin America**
 - **Tetsuo Satoh, PhD – Japan**
 - **S.K. Gupta, PhD, DSc – Asia**
 - **Govinder Flora, PhD – Asia**

- **Toxicology**
- **Chemical engineering and biotechnology**
- **Organic chemistry**
- **Food science**
- **Natural products chemistry**
- **Pharmacognosy**
- **Botanical dietary supplements**
- **Immunology**
- **Cell and molecular biology**
- **Pharmacology**
- **Drug discovery and screening**

Industry Sectors

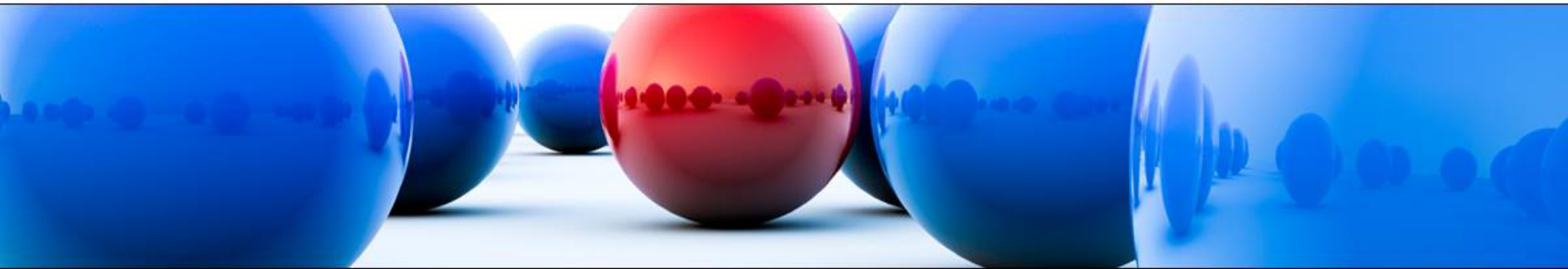
(Safety Assessment and Regulatory Compliance)



- **Foods**
 - **Food Additive Petitions (FAP)**
 - **Generally Recognized As Safe (GRAS)**
 - **New Dietary Ingredient Notifications (NDINs)**
- **Food Contact Substances (FCN)**
- **Health Claim and Structure/Function Claim Substantiation**
- **EU Regulations for Food**
 - **Novel Food Dossier and Notification**

- **United States:**
 - **GRAS Notifications**
 - **GRN# 44, 67, 77, 78, 94, 118, 119, 130, 140, 196, 233, 236, 268, 282**
 - **GRAS Self-Determinations ▶ 60+**
 - **Food Additive approval for glycerol ester of gum rosin**
- **International:**
 - **Food Additive submissions to Canada, the European Union, plus 17 other countries**
 - **Submission to JECFA**

Generally Recognized as Safe Self-Determinations and Notifications (GRAS)



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**

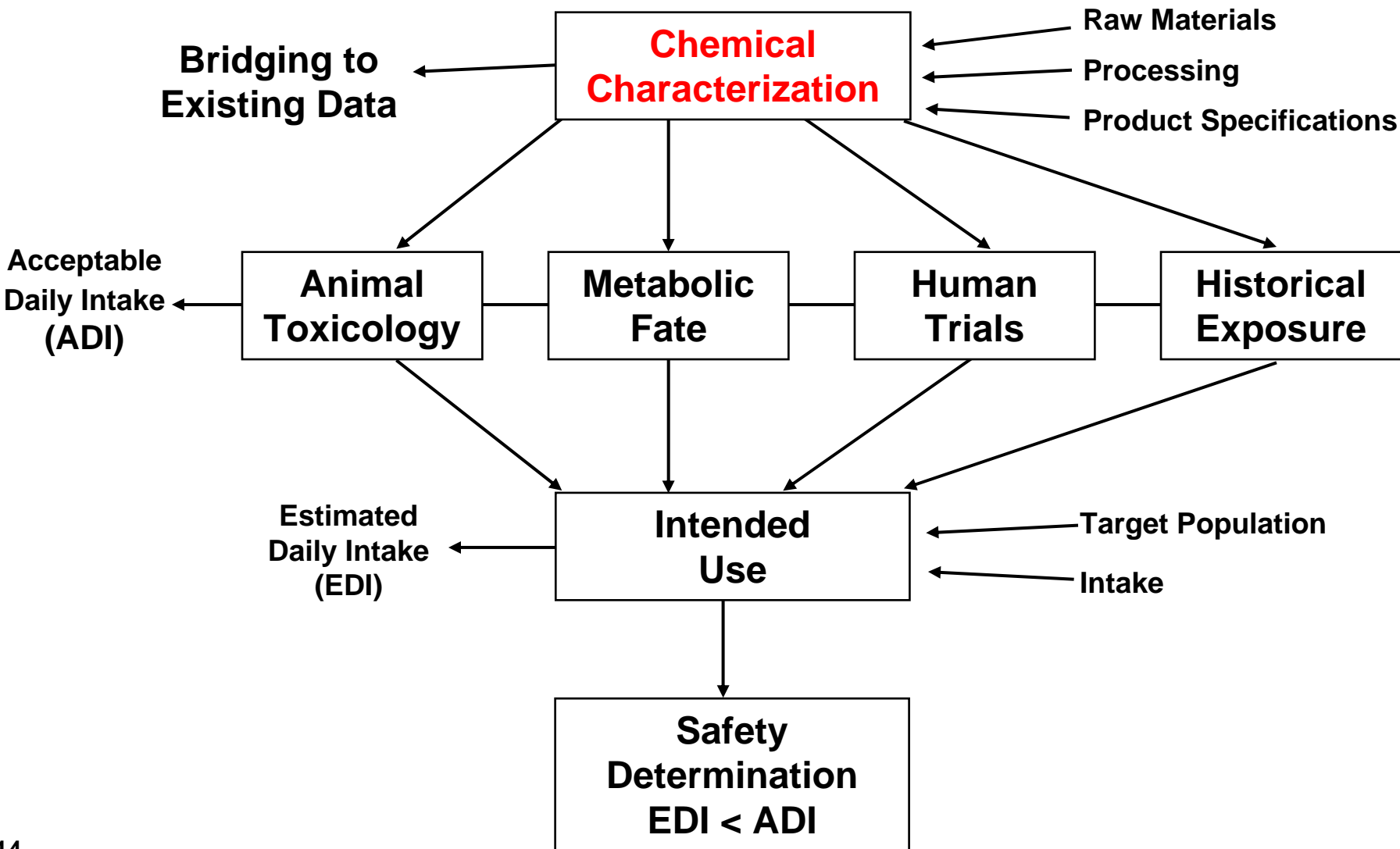
- **Safety standard is the same as that for food additives, “reasonable certainty of no harm”**
- **Evidence of safety is the same as is required to support approval of a food additive petition**
 - **Breadth and quantity of information**
 - **Quality of information**
- **Information must be publicly**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

- **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**
 - **Batch analysis results**
 - **Contaminants detected**
 - **Product stability**

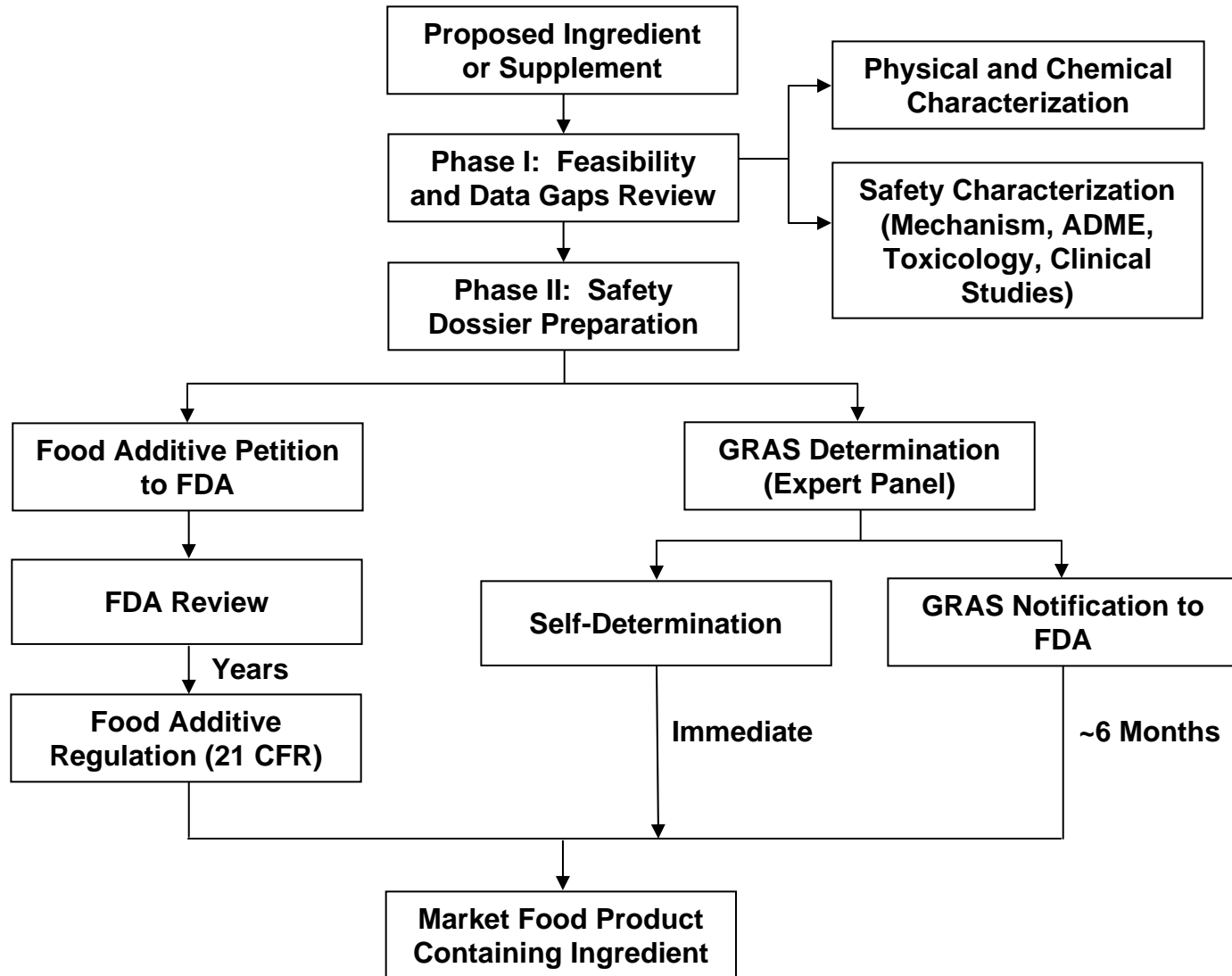
- **Historical Use and Consumer Exposure:** History of use and/or natural occurrence of the GRAS substance in foods; a description of the proposed uses and use levels of the GRAS substance in food. Calculation of estimated daily intake (mean and 90th percentile)
- **Intended Effect:** Characterization of the intended use or functional effect
- **Analytical Methodology:** Method for determining the quantity of the substance in food

- **Safety Data:**
 - **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).**
 - **Corroborative information on safety of other substantially equivalent products is evaluated.**
 - **Includes a review of pivotal published and corroborative unpublished studies (*in vitro*, *in vivo* toxicology, ADME and clinical studies in humans)**

Safety Analysis



Food Regulatory Paths



- **Heightened Congressional and Agency activities focused on danger of chemicals in foods and consumer products**
- **Influential anti-chemical activist groups engaged**
- **Chemophobia reaches the world of food**

- **Cross-cutting themes:**
 - **Need to protect sensitive subpopulations**
 - **Concern over dealing with information from emerging science (endocrine disruption)**
 - **Links between chemical exposures and disease (diabetes, obesity, cancer, ADHD)**
 - **Transparency of approval process**

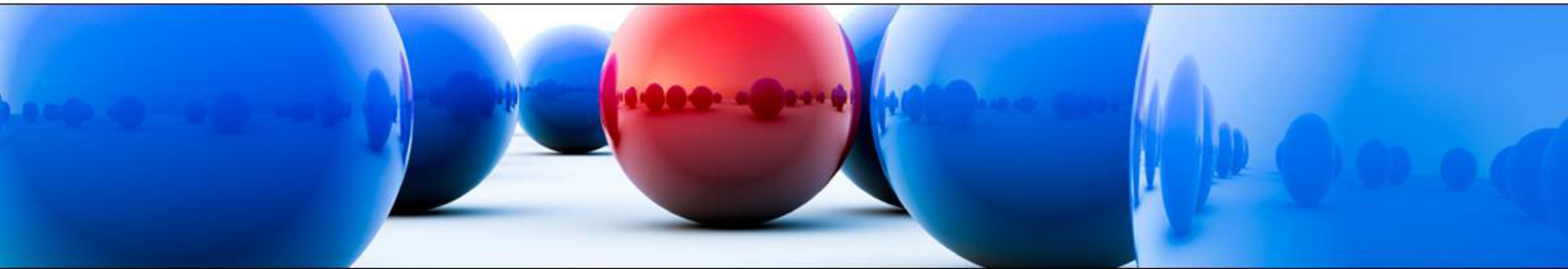
- **Analytical detection methods becoming more sensitive all the time**
- **Bio-monitoring studies finding biomarkers and environmental chemicals in our bodies**
- **Chemical ingredient and scientific issues are the subject of intense media focus**

- **Research Scientists:**
 - **Emerging research indicates biological effects may be observed at low doses**
 - **Is conventional toxicology/risk assessment outdated?**
- **Regulatory Scientists:**
 - **Safety evaluation must be based on data from validated studies that can generate information predictive of human adverse effects**

- **FDA joined the Tox 21 collaboration, which leverages federal agency resources, including research, funding and testing tools, to develop models for more effective chemical risk assessments**
- **Provide the data generated from the innovative chemical testing methods that characterize toxicity pathways to risk assessors to use when making decisions about protecting human health and environment**

- **Original focus on evaluating the safety of existing exposures is shifting to detection and prevention of toxicity and disease through use of data from low dose high throughput screening in human cells**
- **How to distinguish a normal biological change/fluctuation from an adverse effect?**

PEW Health Group's Food Additive Project



Potential Key Takeaways from PEW Initial Review

- **The system is outdated**
 - **It has been more than 50 years since the food law was passed**
 - **A significant shift occurred in the 1990s away from petitions to industry notifications and consultations (“privatization” vs. public transparent process)**
- **It is impossible to really know how much consumers are consuming and what has been FDA-reviewed/approved**
- **It is impossible to assess potential implications for public health**
- **Safety standard – there is no clear definition of what “safe” means; different for different categories**
 - **FDA does not always make the decision – sometimes industry makes the call**

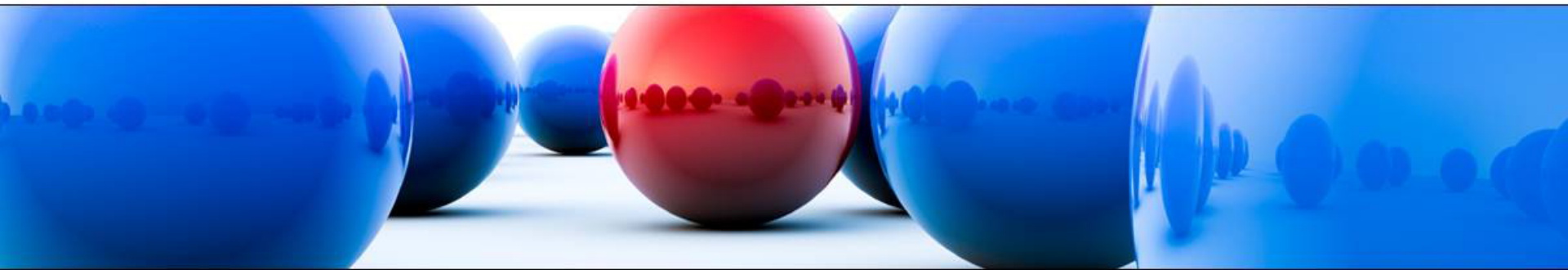
Potential Key Takeaways from PEW Initial Review (continued)

- **The FDA “Redbook”**
 - **May well be missing important emerging endpoints and effects (e.g., endocrine, new effects now detected below NOAEL)**
- **Refining the regulatory process**
 - **FDA should issue clear guidance on incorporation of new methods/kinds of data into GRAS determinations**
 - **Safety decisions (including GRAS affirmations) should be subject to cyclical re-review, during which new science, postmarket surveillance data, and the “human experience” (what is happening in the marketplace with ingredient usage and food consumption) is considered**

SPHERIX CONSULTING'S PUBLICATION

**Kruger, C.L., Booth, N. and Hayes, A.W., “Policing
Ourselves: Is GRAS Robust Enough?,” Food
Technology, pages 18-19, August 2011**

http://www.ift.org/food-technology/past-issues/2011/august/columns/food_medicine_health.aspx



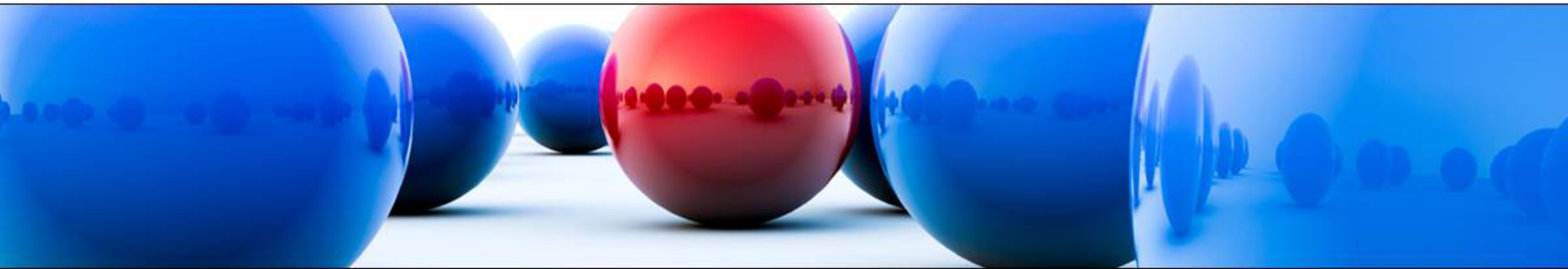
Policing Ourselves: Is GRAS Robust Enough?

- **The public nature of the GRAS determination, relying on published data as the source of the pivotal information, makes the GRAS process the most transparent and, therefore, potentially the most robust and powerful tool currently used worldwide for evaluating new food ingredients**
- **One approach to further strengthen the GRAS process would be for the FDA to seek authority from Congress to require all companies to Notify the FDA of their GRAS determinations**
- **Even without FDA Notification, GRAS is an efficient, robust, transparent, and successful process for evaluating the safety of food ingredients**

- **FDA needs to exercise case-by-case judgment to evaluate food safety**
- **FDA credibility is being eroded**
- **Controversial research findings appear more newsworthy than assessments of safety (“negative” news vs. “positive” findings)**
- **Unless and until new science is properly validated and we understand how to use the findings to assess and manage risk, any substance can be portrayed as “unsafe”**
 - **May pressure regulators to be increasingly precautionary**

- **We need to make sure that the path we are on does not end at the Precautionary Principle**
- **Encouraging development of new science is good, but cannot rely upon non-validated assays that have not been scientifically bridged to human endpoints**

United States Notifications for New Dietary Ingredients (NDI) for Dietary Supplements (DSHEA)



Dietary Supplement Including New Dietary Ingredient

Definitions:

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

New Dietary Ingredient

- A dietary ingredient not marketed in the United States before October 15, 1994
 - And was present in the food supply as an article used for food (either chemically altered or not*)
 - 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 ODI
- Changes that alter the composition of materials used to make the ODI, such as using a different part of a plant

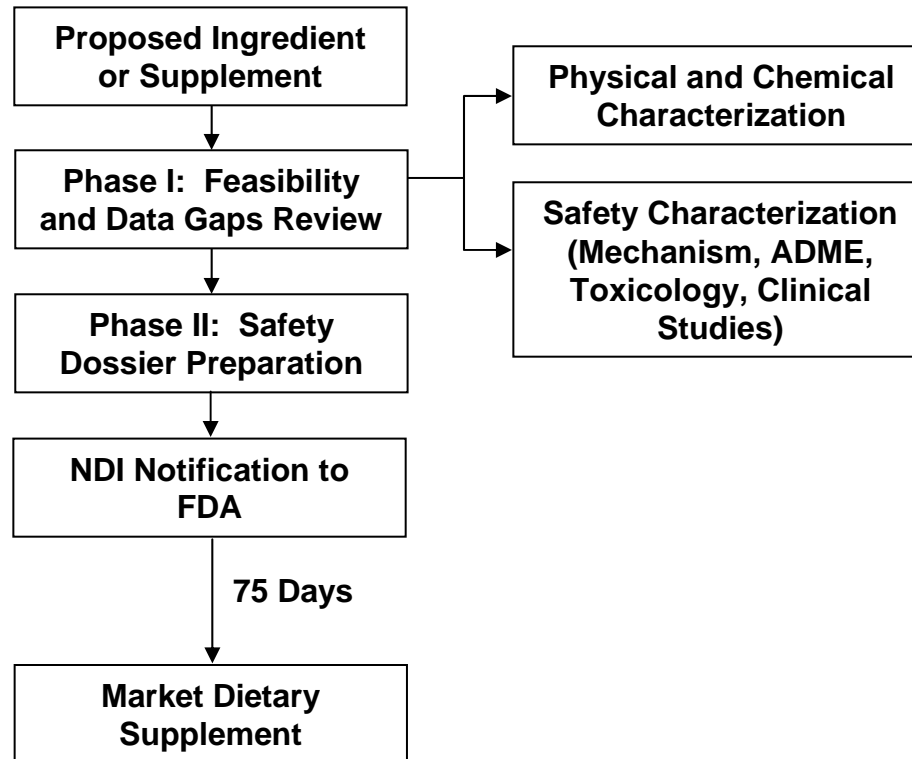
***NDIN not required**

Dietary Supplement Including New Dietary Ingredient

Safety Standard:

- **Safety is defined as: will reasonably be expected to be safe under the conditions of use defined in the labeling**

Food Regulatory Paths



- **There are about 55,600 dietary supplement products on the market in the U.S.**
- **FDA has only received approximately 700 NDI Notifications in 16 years or approximately 50 NDINs per year**
- **FDA's review of NDI notifications are an important preventive control mechanism to ensure that the consumer is not exposed to unnecessary public health risks in the form of new ingredients with unknown safety profiles**

The Role and Responsibility of Industry to Address this Problem:

- **Manufacturers, distributors, importers and others in the supply chain of dietary supplements are responsible for ensuring that their products do not contain new chemical ingredients that have not been studied adequately in humans.**

***Margaret A. Hamburg, M.D.
FDA Commissioner**

- **FDA has “acknowledged” 162 NDI notifications; an acknowledgement means that FDA does not object to the marketing of the ingredient in a dietary supplement under the conditions of use proposed in the notification**
- **To date FDA has objected to 450 notifications**
- **Many products described in the 450 objectionable NDINs are have found their way to the market**

- **The guidance is intended to inform and assist manufacturers, distributors, and other industry entities in deciding when a premarket safety notification for a dietary supplement containing a new dietary ingredient (NDI) is necessary and in preparing premarket safety notifications.**
- ***“Guidance represents the 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.”***

- **“The NDI safety standard is different than the standard for food additives, drugs, pesticides, and other FDA-regulated products. Recommendations in guidance documents that are tailored to the safety assessment needs of other FDA-regulated products may not always be appropriate for dietary ingredients and dietary supplements.”**
- **“You should use your own best judgment in compiling scientific evidence that provides a basis to conclude that the NDI that is the subject of your notification will reasonably be expected to be safe when used under the conditions recommended or suggested in the labeling of the dietary supplement described in the notification.”**

<http://www.fda.gov/food/guidancecomplianceregulatoryinformation/guidancedocuments/dietarysupplements/ucm257563.htm>

- **Is it a dietary ingredient?**
- **Is it new?**
- **Is it subject to notification?**
- **What information should be submitted?**

Is the Ingredient New? (NDIN required)

- **An herb/botanical introduced in U.S. after DSHEA**
- **An herb/botanical in U.S. before DSHEA but not as a dietary ingredient (only in/as conventional food, drug, or non-food)**
- **An herb/botanical concentrate, metabolite, constituent, extract, or combination, if:**
 - **Introduced in U.S. after DSHEA**
 - **Used in U.S. before DSHEA but not as dietary ingredient; or an extract of an old dietary ingredient with solvent other than water or aqueous ethanol or any change to manufacturing process that alters its chemical composition or structure**

Definition of NDI and Requirement for NDIN

	NDI	NDIN
• A dietary ingredient < DSHEA	No	No
• A dietary ingredient > DSHEA and present in the food supply	Yes	
a) not been chemically altered	Yes	No
b) been chemically altered	Yes	Yes
• A dietary ingredient > DSHEA and not present in the food supply	Yes	Yes

A NDIN is NOT required if:

**The Dietary Ingredient is listed or affirmed by
FDA as GRAS, self-affirmed as GRAS, or
approved as a direct food additive in the U.S.**

- **If it is a dietary supplement contains a new dietary ingredient for which there is inadequate information to provide reasonable assurance that such ingredient does not present a significant or unreasonable risk of illness or injury**
- **FDA defines unreasonable risk as:**
 - **Burden of proof is met “*when product’s risks outweigh its benefits in light of the claims and direction for use in the products labeling or conditions of use*”**
 - **“*In the absence of a benefit, even a small risk may be unreasonable*”**

- **FDA posed the following questions to identify risk for a NDI:**
 - **What additional data is needed to fortify existing data on the ingredient?**
 - **Completely new, likely not enough existing data to identify predicted risk (i.e. if you have no information how do you establish a reasonable expectation of safety?)**
 - **History of use, likely doesn't give long term chronic data, sometimes it may not provide daily data. How can these gaps be addressed?**
 - **Proposed conditions of use comparable to documented history of use?**

- **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**

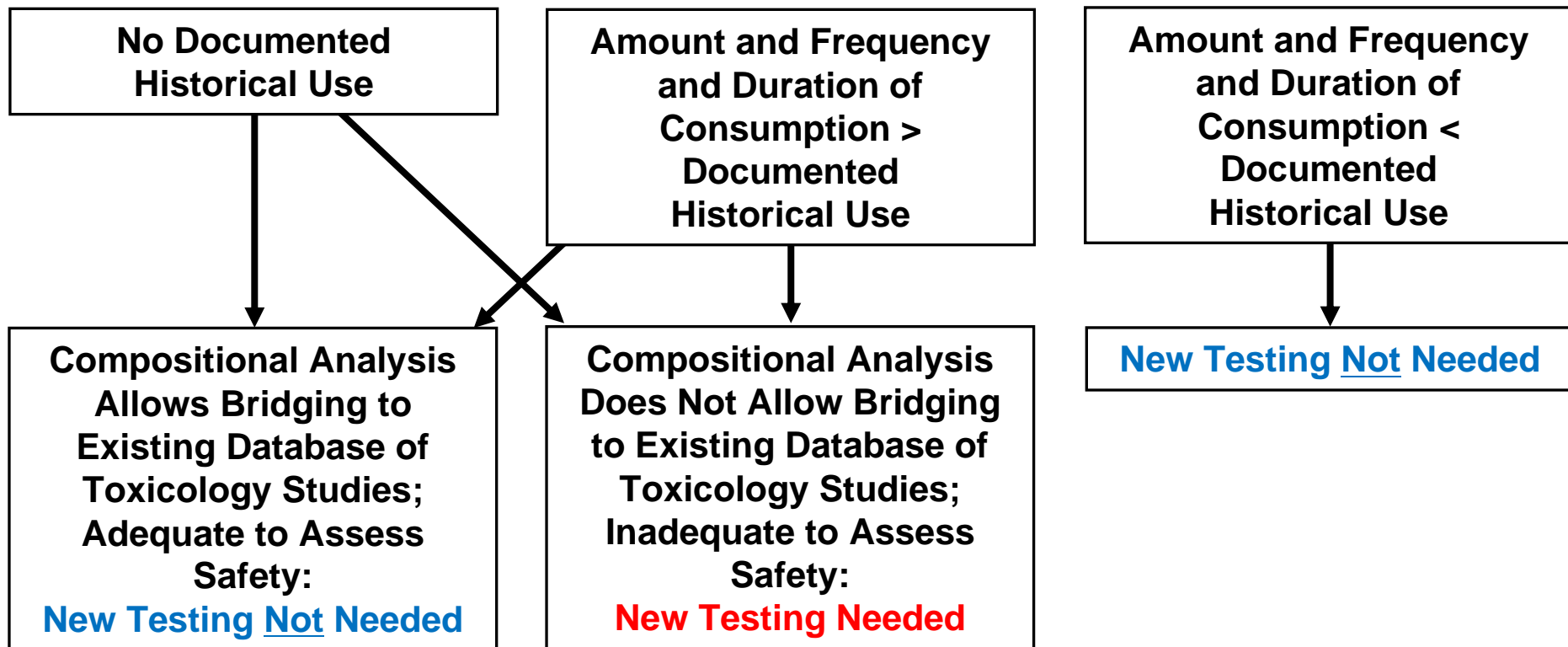
Comprehensive Safety Profile for the NDI

- **Toxicology Studies**
- **Human Studies**
- **Other Studies**
- **History of Use**
- **Other Evidence of Safety**
- **Other Safety and Toxicology References**

What Necessitates Toxicology Testing for an NDI?

- **Is there any historical use in the U.S.?**
- **Are current intake levels or recommended intake levels different from historical use?**
- **Is the historical duration and frequency of use consistent with historical use?**
- **Is the historical indication consistent with historical use?**
- **Has the target population changed?**
- **Has the traditional delivery matrix been altered or eliminated? (chemical or compositional change)**
- **If there are traditional cautions in the use of the NDI, are these cautions communicated to the consumer?**
- **Are there other reasons to expect a different toxicity profile for the proposed formulation versus the traditional preparations?**

Decision Tree Approach for Toxicology Testing New Dietary Ingredient



- **Animal toxicology is a tool: classic rodent studies evaluate toxicity**
- **Animal models must be chosen appropriately to extrapolate to the human, including consideration of:**
 - **Bioavailability**
 - **Nutritional requirements/limitations**
 - **Metabolic parameters**
 - **Developmental stage**
- **Study must be designed to prevent differences in pharmacokinetic handling or dietary imbalance from confounding toxicology results**
- **Strengths**
 - **Well controlled experiments, controlled doses, no confounding exposures issues**

Safety Testing Recommendations

Draft Guidance

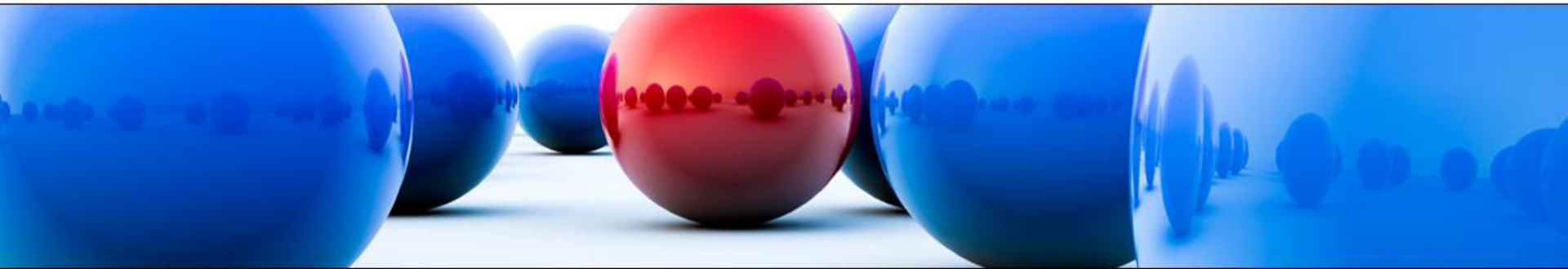
- **Genotoxicity Battery**
 - **Bacterial mutagenesis, *in vitro* cytogenetics, *in vivo* mammalian test**
- **Repeat dose toxicity**
 - **14-day Range-Finding**
 - **90-Day Subchronic**
- **Chronic/Carcinogenicity**
- **Reproductive**
 - **One generation; Multi-generation**
- **Developmental/Teratology**
- **ADME**

Toxicology Testing Can Inform Us About:

- **Hepatotoxicity**
- **Nephrotoxicity**
- **Cardiovascular toxicity**
- **Pulmonary toxicity**
- **Dermal toxicity**
- **Ocular toxicity**
- **Developmental toxicity**
- **Neurotoxicity**
- **Behavioral toxicity**
- **Immunotoxicity**
- **Hematopoietic toxicity**
- **Reproductive toxicity**
- **Endocrine organ toxicity**
- **Gastrointestinal toxicity**

- **Local and systemic effects**
 - **At site of first contact (gastrointestinal)**
 - **At site(s) distal to point absorbed (internal organ damage)**
- **Reversible and irreversible effects**
 - **Disappear following cessation of exposure (enzyme changes, respiratory depression)**
 - **Persist or even progress after exposure is discontinued (cancer, genetic alterations, birth defects, death)**
- **Immediate and delayed effects**
 - **Develop shortly after single exposure (cyanide poisoning)**
 - **Occur after a lapse of time (10-20 years for cancer)**

United States Regulatory Pathways: Compare and Contrast



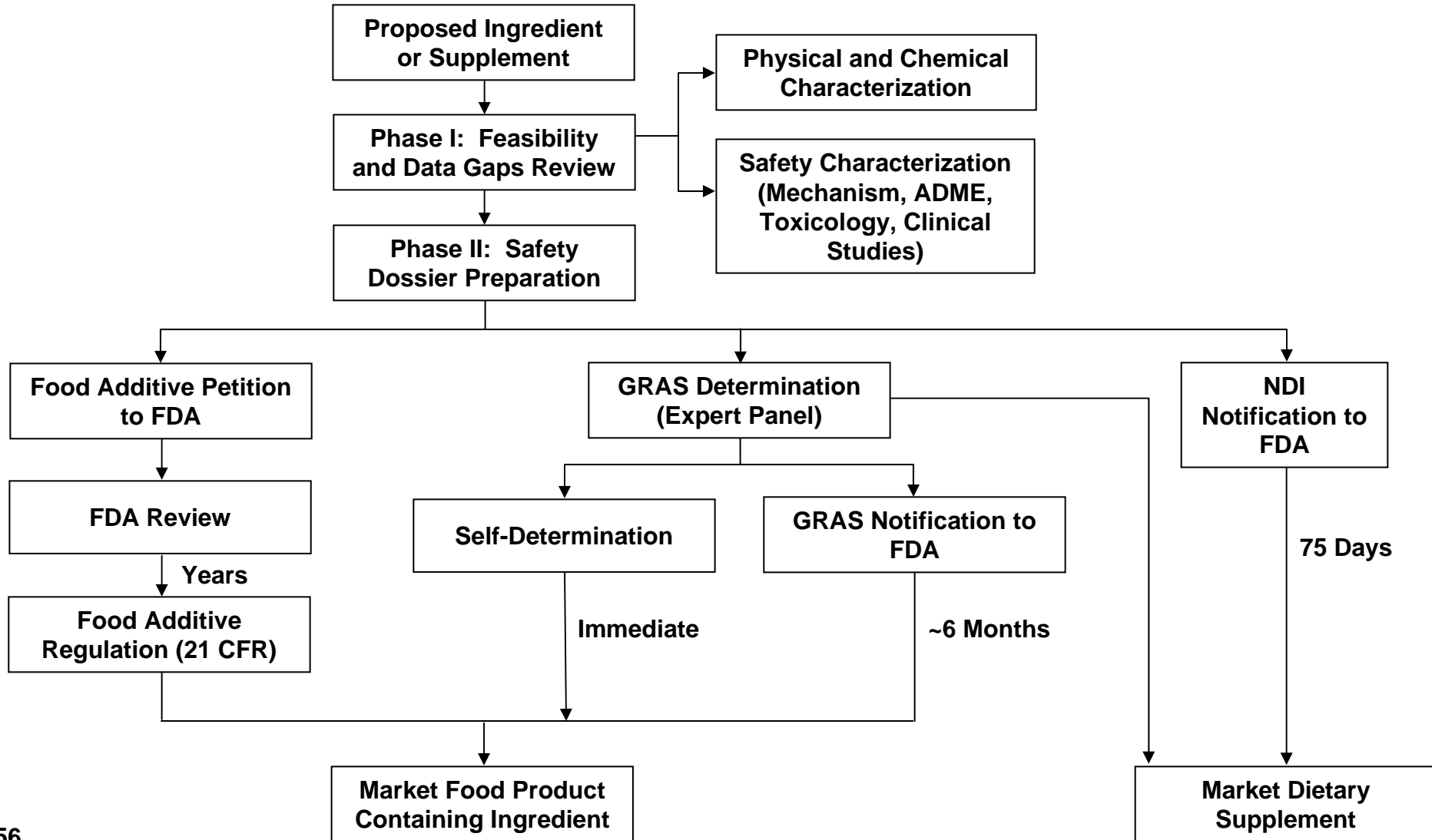
Foods: Comparison of Regulatory Paths

FOOD ADDITIVE	GRAS	Dietary Supplement
Federal Food, Drug, and Cosmetic Act 1938	Exemption to Food Additives Food Additives Amendment 1958 Notification Process Promulgated 1997	DSHEA 1994 Draft Guidance for Industry 2011
Food Additive Petition	General Recognition of Safety by Expert Panel: GRAS dossier (self-GRAS or Notification)	Pre-1994: No FDA Notification Post-1994: New Dietary Ingredient (NDI) Notification to FDA
Information and data may be unpublished	Pivotal Information and data must be published	Information and data may be unpublished
Assumes lifetime exposure	Assumes lifetime exposure	Duration and frequency of exposure dictated on label
Can not exclude sub-populations	Can not exclude sub-populations	Can target and exclude sub-populations on the label

Foods: Comparison of Regulatory Paths

FOOD ADDITIVE	GRAS	Dietary Supplement
EDI based on specific food uses and levels calculated using databases to derive mean and 90 th percentile consumption	EDI based on specific food uses and levels calculated using databases to derive mean and 90 th percentile consumption	EDI based on recommended use and levels as defined in the labeling
Reasonable certainty of no harm SPECIFIC TO USE/INTAKE	Reasonable certainty of no harm SPECIFIC TO USE/INTAKE	Reasonably expected to be safe under the conditions of use defined in the labeling
FDA makes the determination of safety based on data provided by submitter.	General Recognition of Safety based on publicly available data and consensus of expert panel opinion	Burden is on the submitter to establish safety for NDI under the conditions of use defined in the labeling. Scientific bar has been raised.
FDA pre-market approval required	No FDA pre-market approval	No FDA pre-market approval
Published in 21 CFR	Record of Voluntary Notification and outcome on FDA website	Record of the Mandatory Pre-market Notification and outcome on FDA website

Food Regulatory Paths





Thank you!

www.spherix.com