



NDI GUIDANCE SEMINAR:

*Understanding the
New Safety Paradigm*

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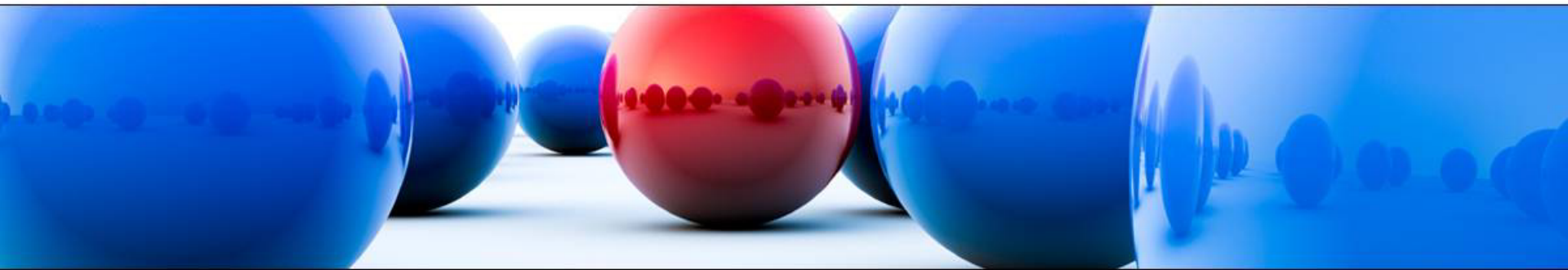
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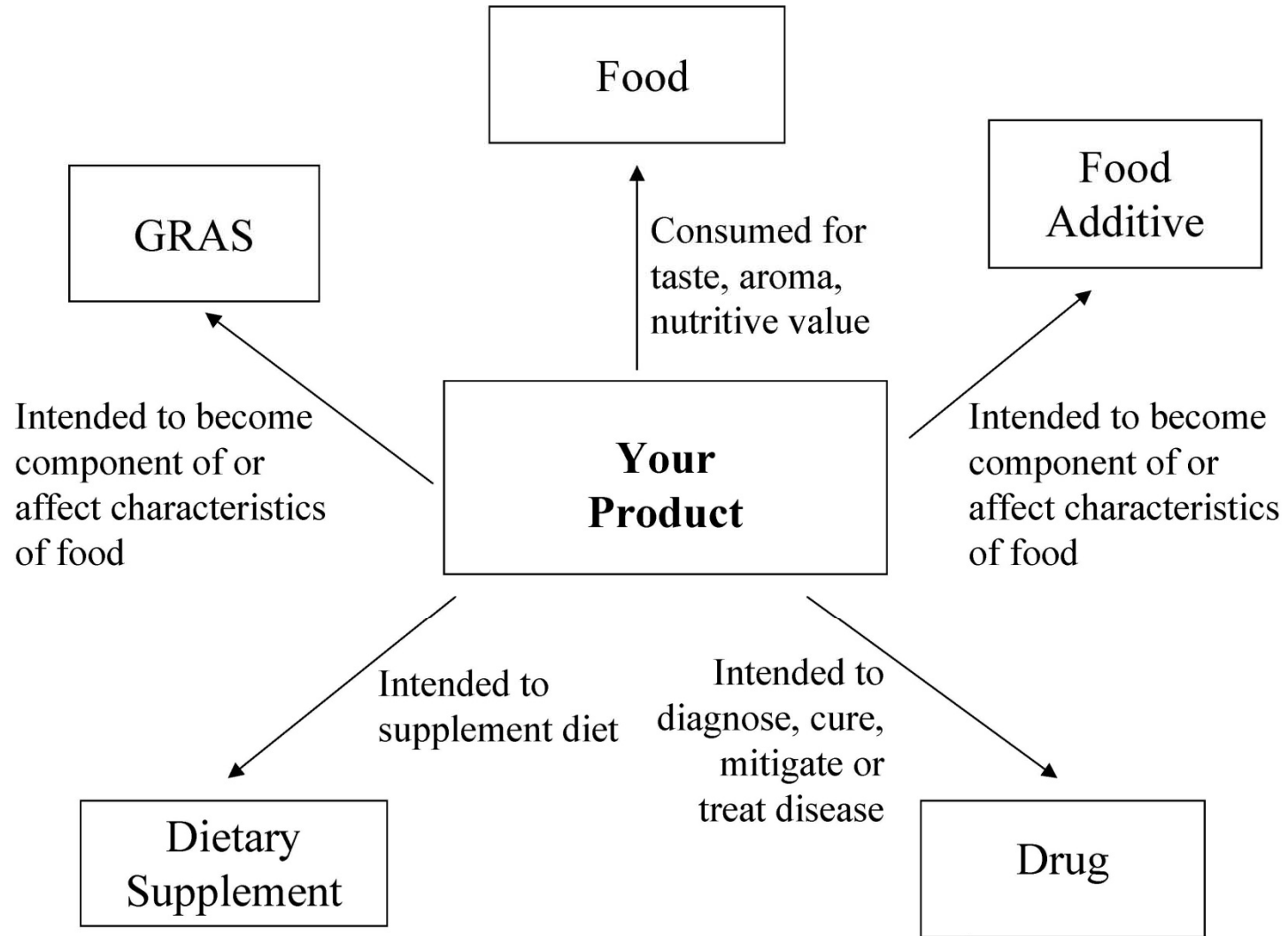
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Draft Guidance for Industry:

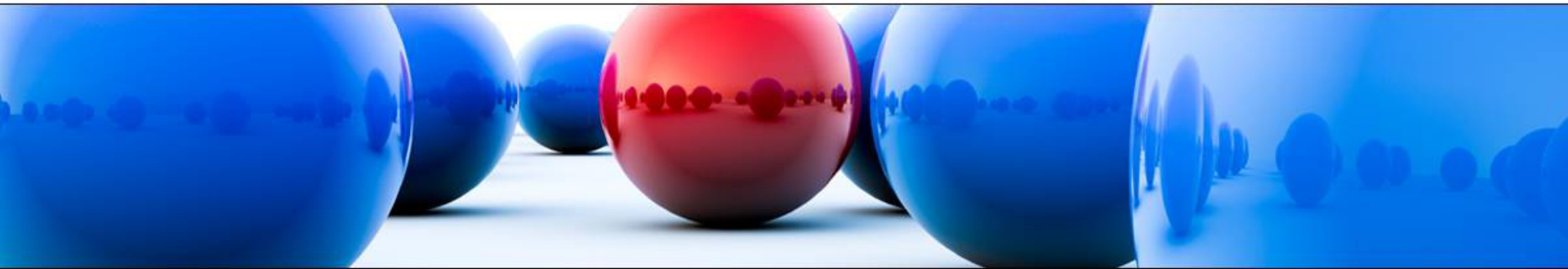
Dietary Supplements: NDIN and Related Issues

GRAS Affirmation and NDIs: What is the Difference? When and How to Use GRAS vs. NDI, and Understanding the Food Ingredient/Dietary Ingredient Distinction





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

- 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**

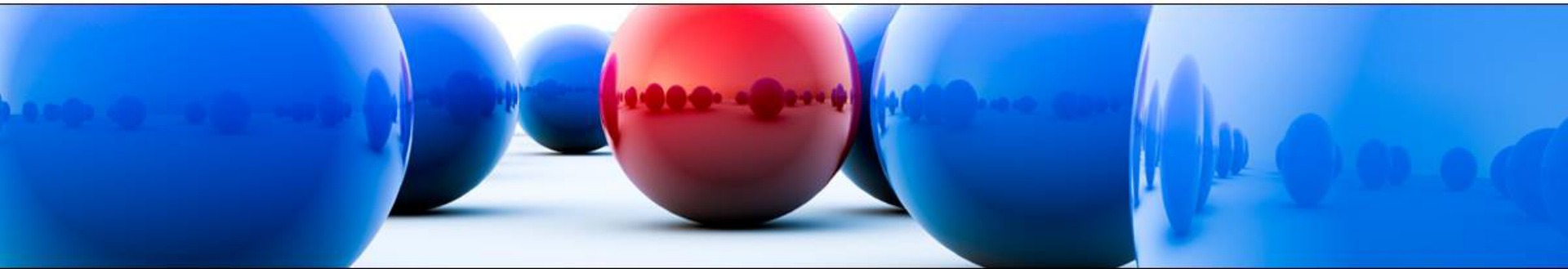
NDIN: Elements of Safety Assessment

- **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**

Comprehensive Safety Profile for the NDI

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

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**

- **Pre-1997**
 - **Self-determination**
 - **FDA Petition**
- **Post-1997**
 - **Self-determination**
 - **FDA Notification**

- **FDA has no questions 😊**
- **Notice does not provide a basis for a GRAS determination 😞**
- **At notifier's request, FDA ceased to evaluate the notice**

- **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)

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

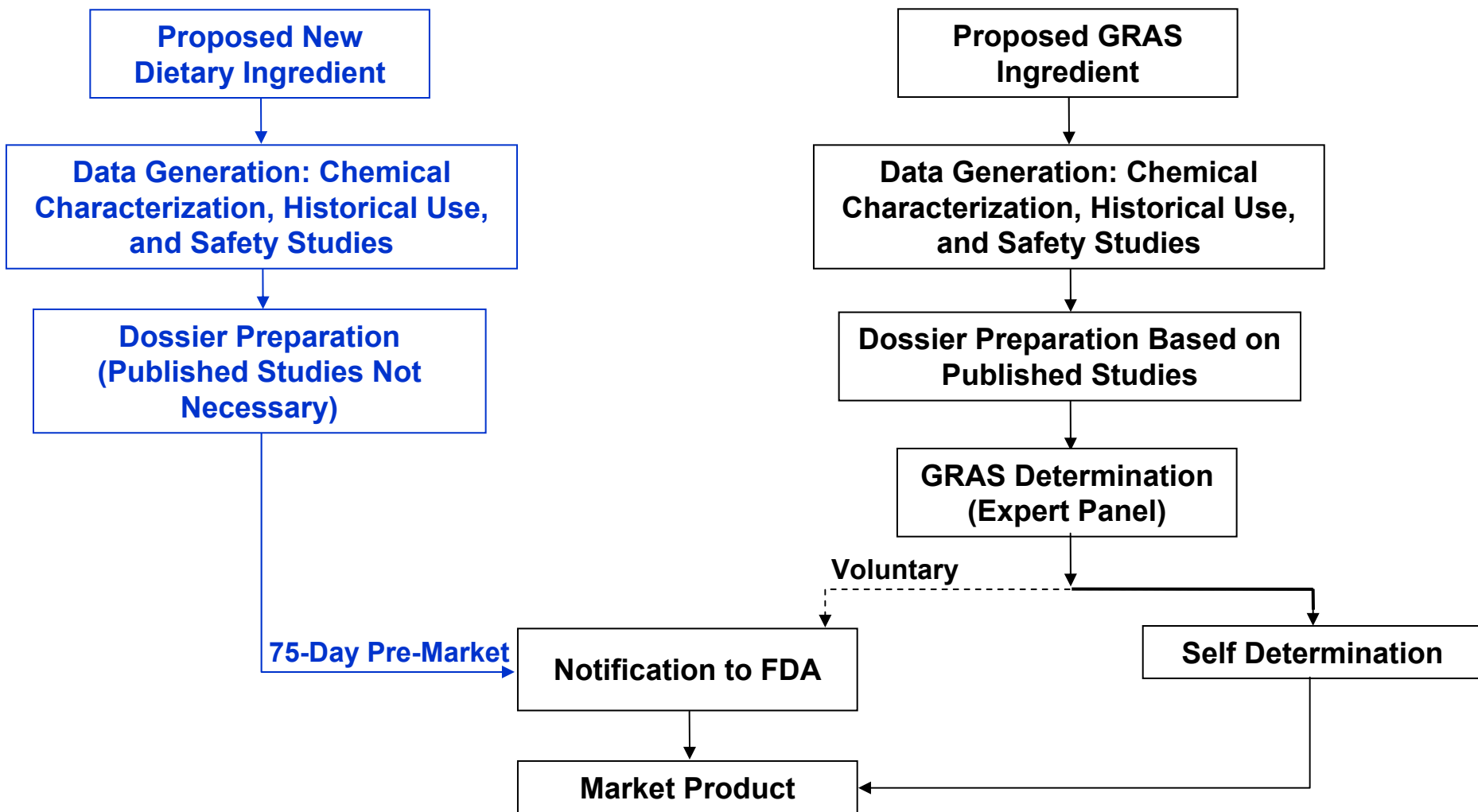
Comparison of Regulatory Paths

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

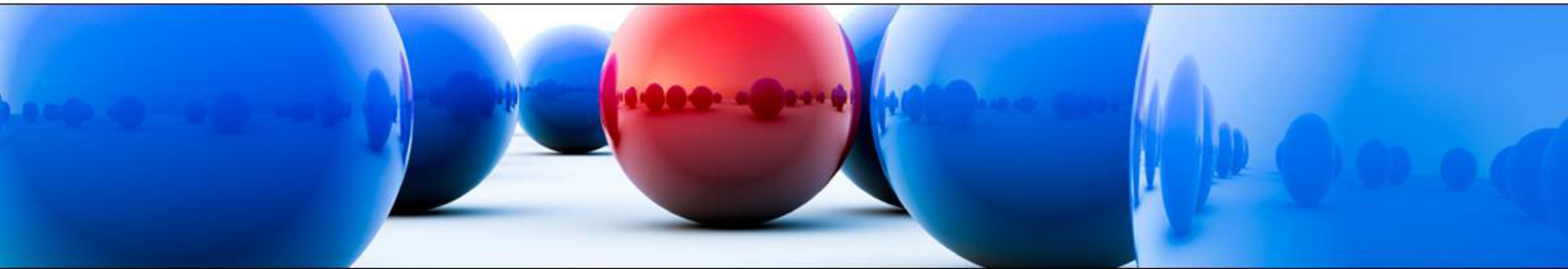
Product Examples

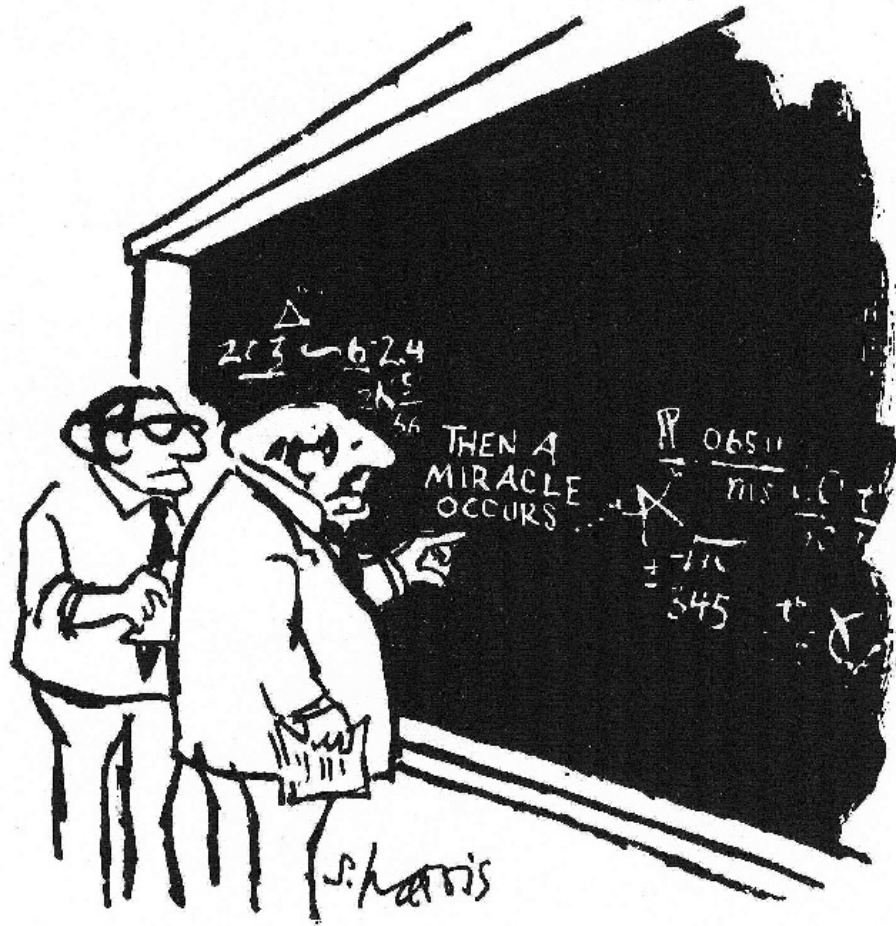
FOOD ADDITIVE	GRAS	Dietary Supplement
Microorganisms either present or not present in the food supply as an article used for food	Microorganisms either present or not present in the food supply as an article used for food	Only microorganisms present in the food supply as an article used for food
Synthetic copy of a constituent or extract of an herb or other botanical ingredient (Synthetic duplicates of natural products)	Synthetic copy of a constituent or extract of an herb or other botanical ingredient (Synthetic duplicates of natural products)	Only a constituent extracted from the botanical or extract of an herb or other botanical ingredient (Natural product)

Summary of Regulatory Paths NDI and GRAS



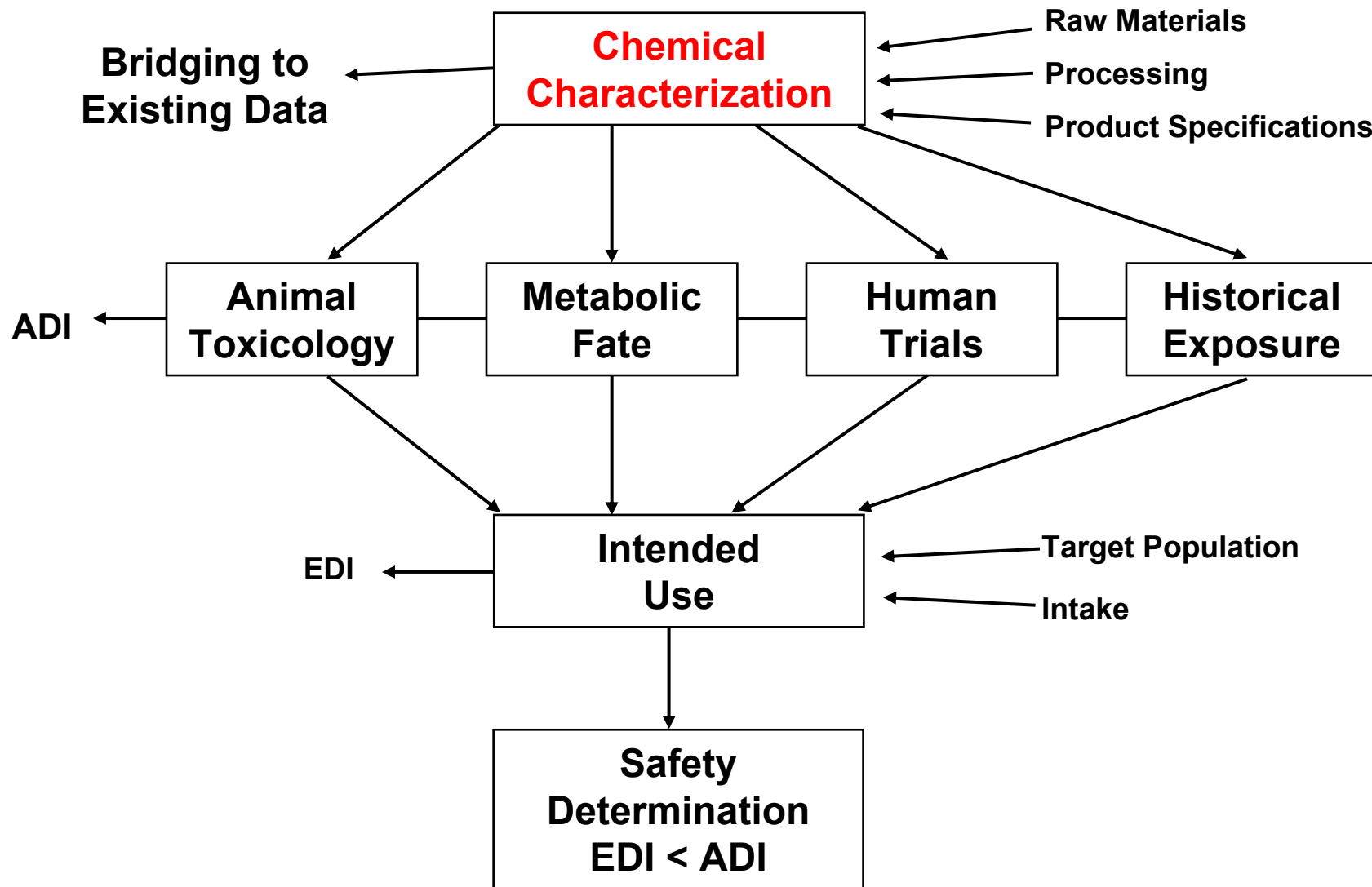
NDI or GRAS Ingredients: Safety evaluation process: Meeting the safety standard





"I think you should be more explicit here in step two."

Safety Analysis



- **Raw Material Source(s) Identity**
- **Production Process**
- **Chemical Characterization**
- **Final Product Specifications and Batch Consistency**
- **Historical Exposure/Human Studies**
- **Toxicology/Safety Study Assessment**
- **ADME**
- **Estimate of Intake**

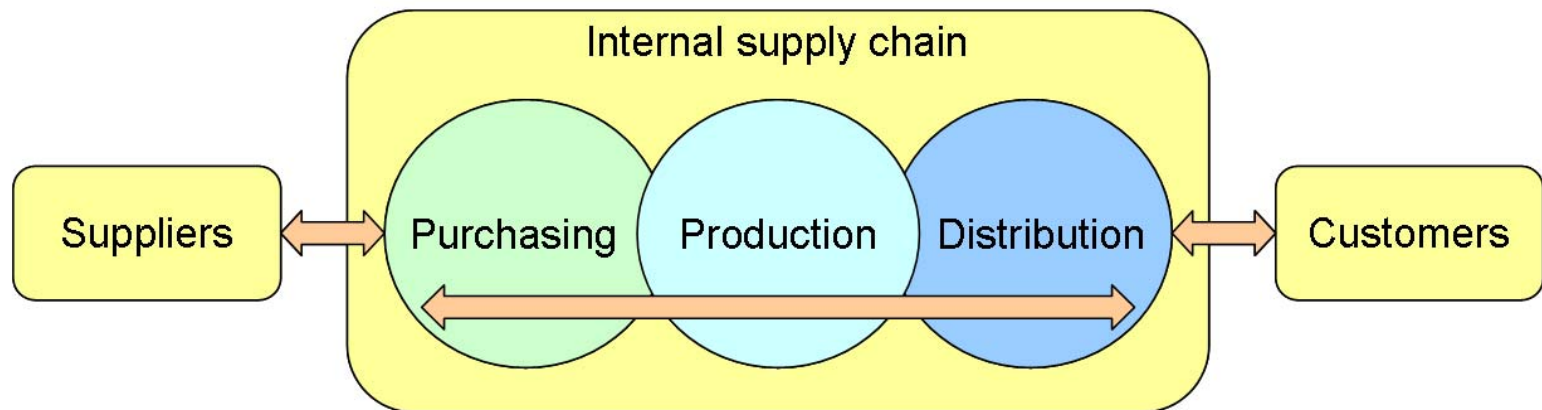
Natural Products Vary in Form and Complexity

- **Raw natural products**
- **Extracts**
- **Semi-purified products**
- **Isolated, purified compounds**

Documentation of Safety Begins With Product Stewardship

In other words:

The *entire* supply chain must be controlled.



➤ Elements of Control

- **Good Agricultural Practices**
- **Raw source material authentication**
- **Retaining voucher specimens**
- **Analytical Testing (HPLC/LC-MS)**
- **Quantitation of marker compounds**
- **Contaminant testing (heavy metals, pesticides, microbes)**
- **Good Manufacturing Practices and documented Standard Operating Procedures**
- **Use of approved food-contact materials (packaging and processing aids (filters, equipment, enzymes))**



Natural Products Vary in Form and Complexity

- **Raw natural products**
- **Extracts**
- **Semi-purified products**
- **Isolated, purified compounds**

Plant Material Authentication and Quality Control

➤ **Bulk lot of material**

- **Collect and archive voucher specimen**



➤ **Should carry out on the bulk lot:**

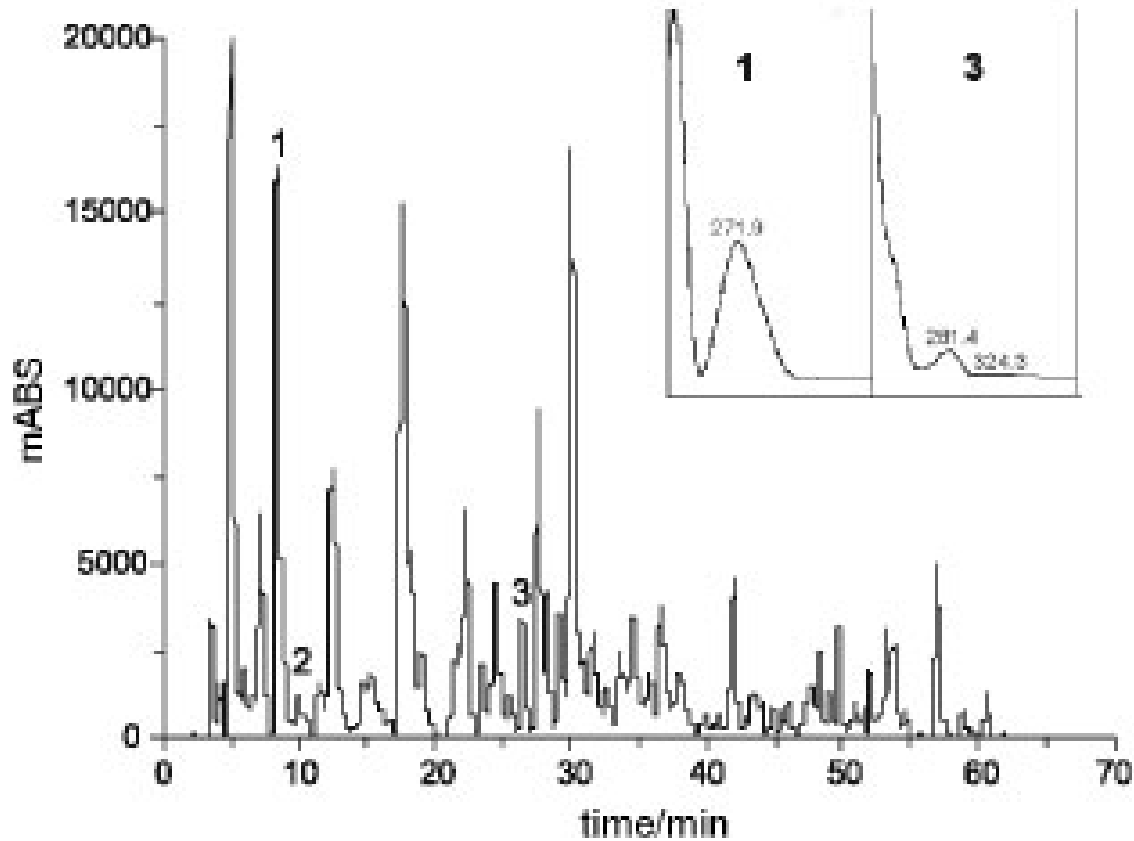
One or more positive identity tests: specific botanical characteristics; species-specific marker compounds; genetic or microscopic analyses

Exclusionary tests: exclusion of potential adulterant or weed species; pesticide residues; heavy metals; mycotoxins; microbes; other pollutants that may be present

Natural Products Vary in Form and Complexity

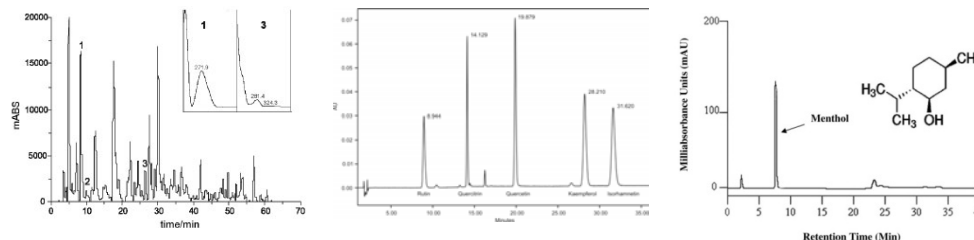
- **Raw natural products**
- **Extracts**
- **Semi-purified products**
- **Isolated, purified compounds**

Extracts: Chemically Complex



Extract/Fraction/Pure Compound Quality Control

➤ Should carry out:



✓ **One or more positive identity tests: presence and appropriate level of species-specific marker compounds**

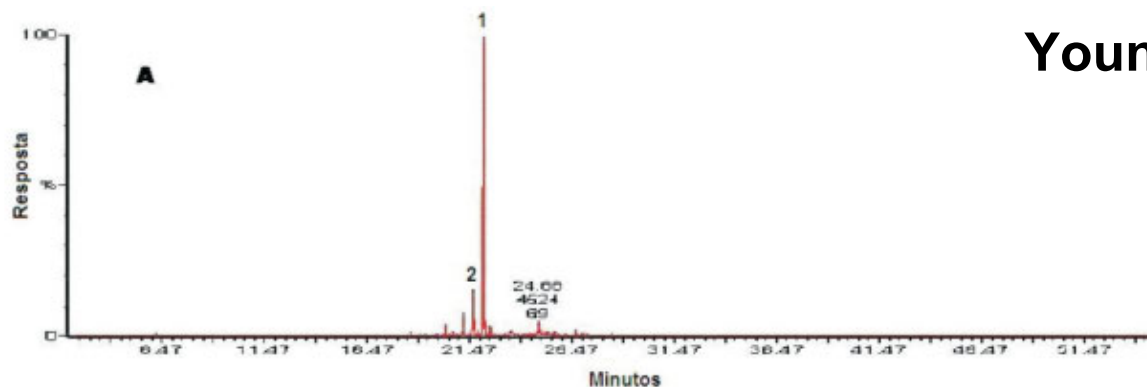
- Also need to establish the natural variation of key compounds as present: define their range of concentrations

⊘ **Exclusionary tests: exclusion of potential adulterant pure compounds (e.g., pharmaceuticals) or species; residual solvent(s); pesticides; heavy metals; mycotoxins; microbes; other pollutants that may be present**

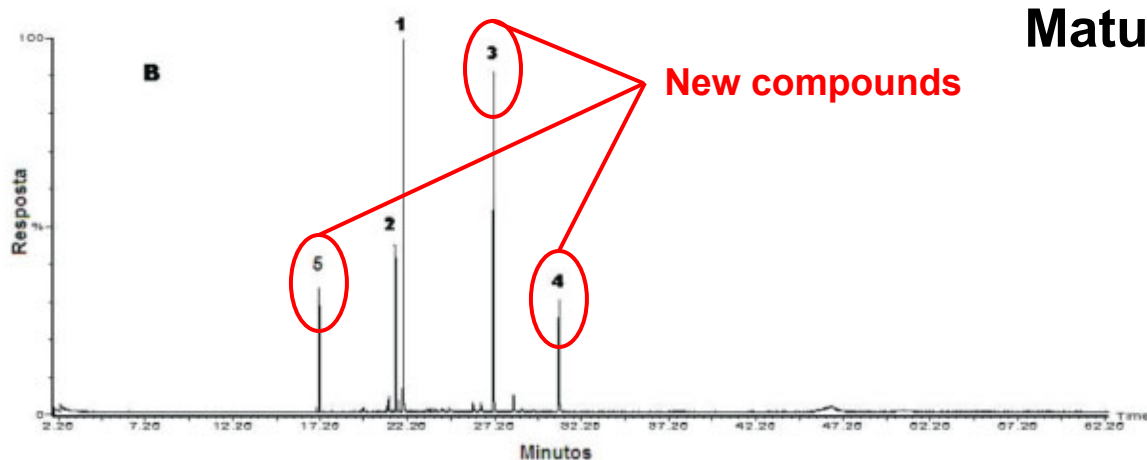
Changing the Ingredient

- **Changing Starting Materials**
- **Changing Extraction Solvent**
- **Altering Chemical Structures**
- **Changing Manufacturing Methods**
- **Isolation and Purification of Compound from Natural Source Versus Chemical Synthesis *de novo***

New Starting Materials Change Chemical Composition

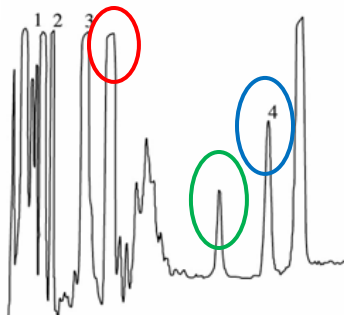


Young leaves

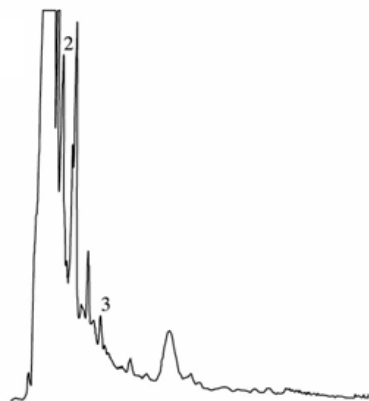


Mature leaves

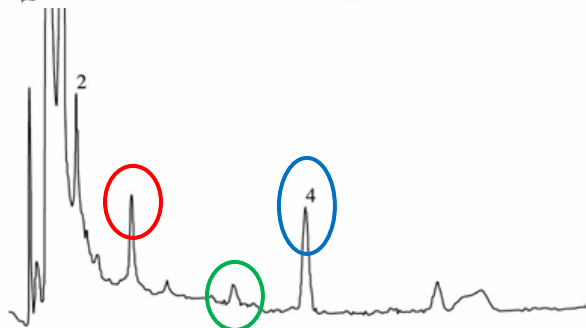
A New Solvent Can Change Chemical Composition



Fresh garlic



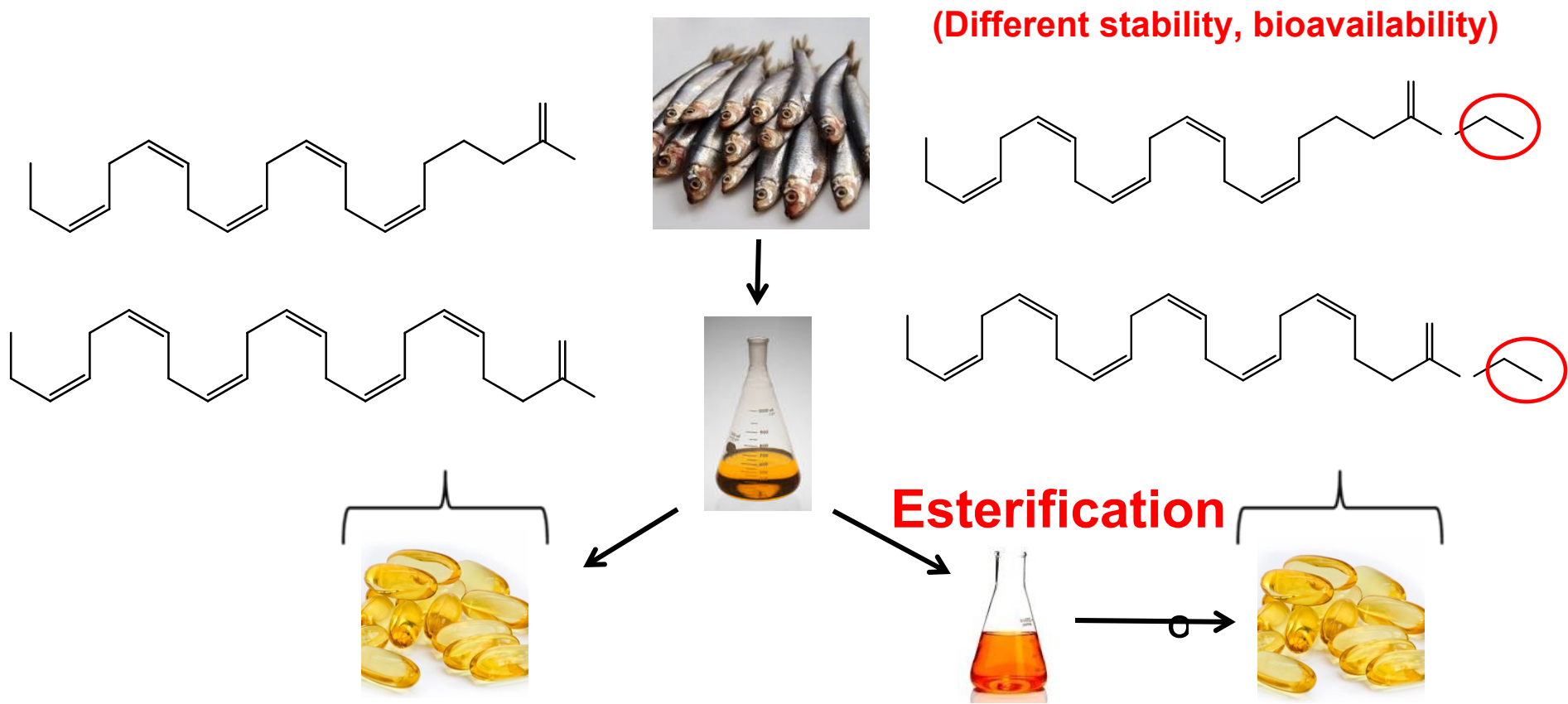
Ethanolic extract



Supercritical CO₂
(More like fresh garlic)

New Process Can Alter Chemical Structure

Example: Esterification of fish oils produces different molecules



New Manufacturing Method and Source Can Change Chemical Composition

Process #1

Ground, dried chicory root



↓ Isolation, purification

Inulin

**Hydrolysis
(breaking-down
process; dissociating
chemical bonds)**

↓ Extracellular,
thermostable inulinase
from *Aspergillus
fumigatus*

**Short-chain FOS + 10%
oligosaccharides**

Process #2

Sucrose from
sugar beet or
cane sugar



**Synthesis
(building-up
process; forming
chemical bonds)**

↓ Fructose +
Beta-fructofuranosidase
from *Aspergillus niger*

**Short-chain FOS (99%
pure)**

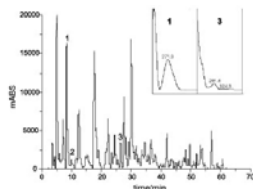
Contaminant Profiles of Naturally-Sourced vs. Synthetically-Produced Pure Compounds Differ

Isolation from natural source

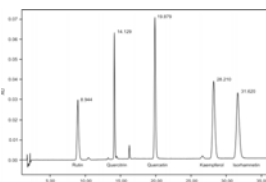
Ground, dried
plant material



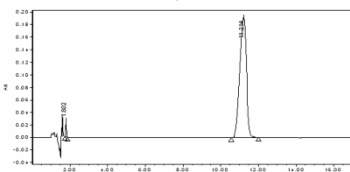
Crude aqueous
ethanolic extract



Chromatography
column fraction
(aqueous ethyl
acetate)



≥ 95% Pure
compound A



De novo synthesis

Starting material

↓
Reagent X,
Hexanes

Intermediate E (90% yield)

↓
Reagent Y,
Ethyl acetate

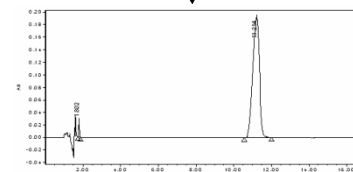
Intermediate F (85% yield)

↓
Chromatography column
Z, Aqueous ethanol

↓
Filtration
step

↓
Solvent
removal

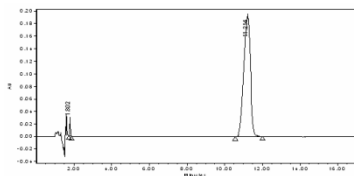
≥ 95% Pure
compound A



Contaminant Profiles of Naturally-Sourced vs. Synthetically-Produced Pure Compounds Differ

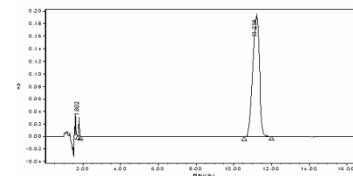
Isolation from Natural Source

≥ 95% Pure compound A



De novo synthesis

≥ 95% Pure compound A



Possible contaminants ($\leq 5\%$, total):

Aflatoxins

Heavy metals

Pesticides

Residual ethanol (solvent)

Residual ethyl acetate (solvent)

Solid chromatography support particles/leached chemicals

Filter leachate chemicals

Chemical contamination from food contact materials (packaging)

Microbes

Moisture

Heavy metals

Unreacted starting material, intermediates E and F

Reagent X

*Undesired reaction products ► May need to characterize!

Residual hexanes (solvent)

Reagent Y

Residual ethyl acetate (solvent)

Solid chromatography support particles/leached chemicals

Residual ethanol (solvent)

Filter leachate chemicals

Chemical contamination from food contact materials (packaging)

Microbes

Moisture

What Is a Specification?

Used to establish identity and control levels of components, including those relevant for establishing the basis for safety

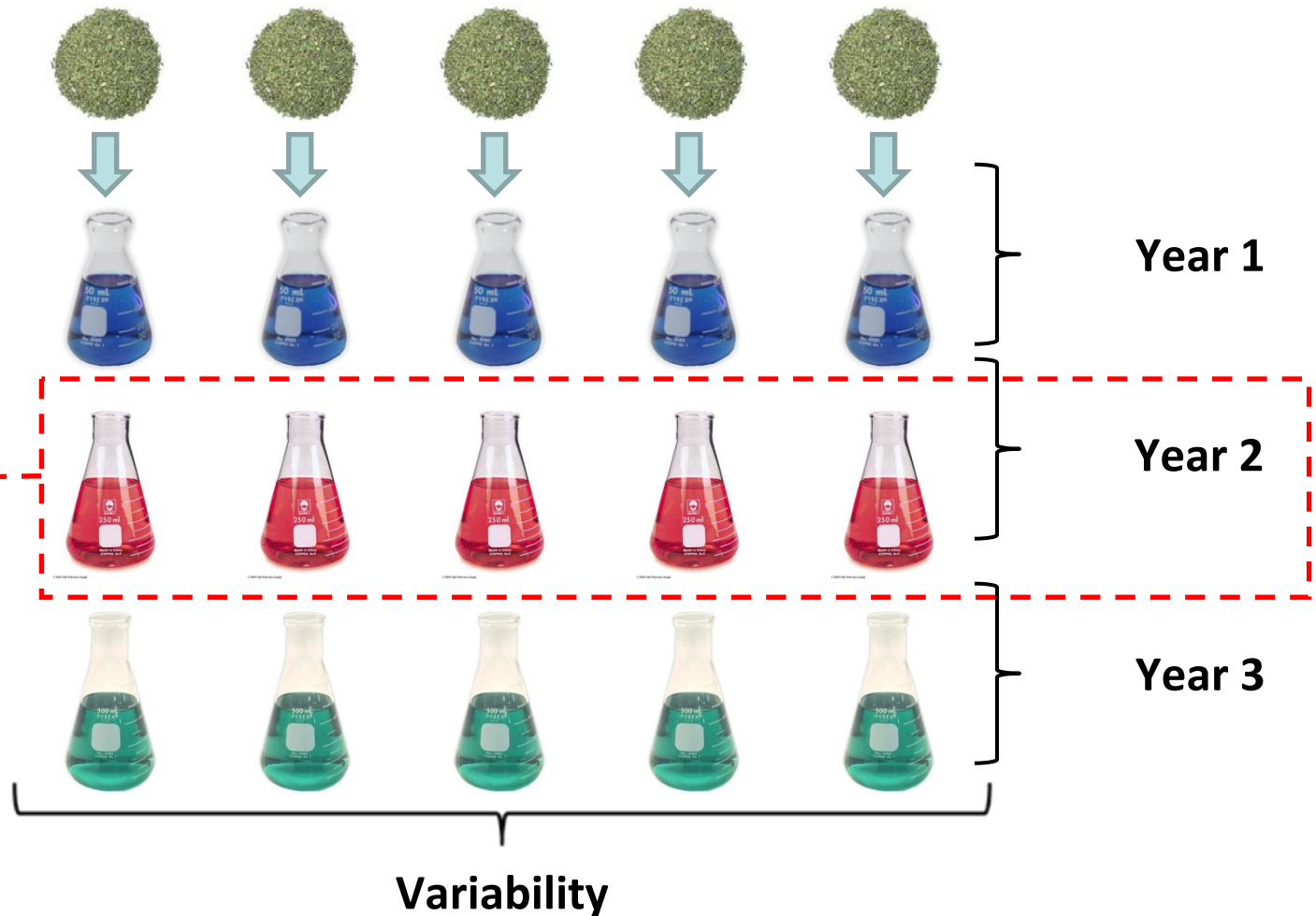
Why? Control Product NOT Process

- **Includes critical safety and identity attributes with acceptance criteria (numerical limits or ranges) and validated analytical methods**

- **Use of “fingerprint” analysis of complex spectra or chromatography of mixtures does not require identification of peaks, but does require matching sufficient numbers of peaks across the entire spectrum or chromatogram to assure the validity of the test result**
- **Components that are known to be toxic can be identified by a single acceptance criteria (“less than”)**

Specifications ensure batch-to-batch consistency for the product

Drought year:
plants and their
derived
extracts may
contain more
defense/stress
compounds.

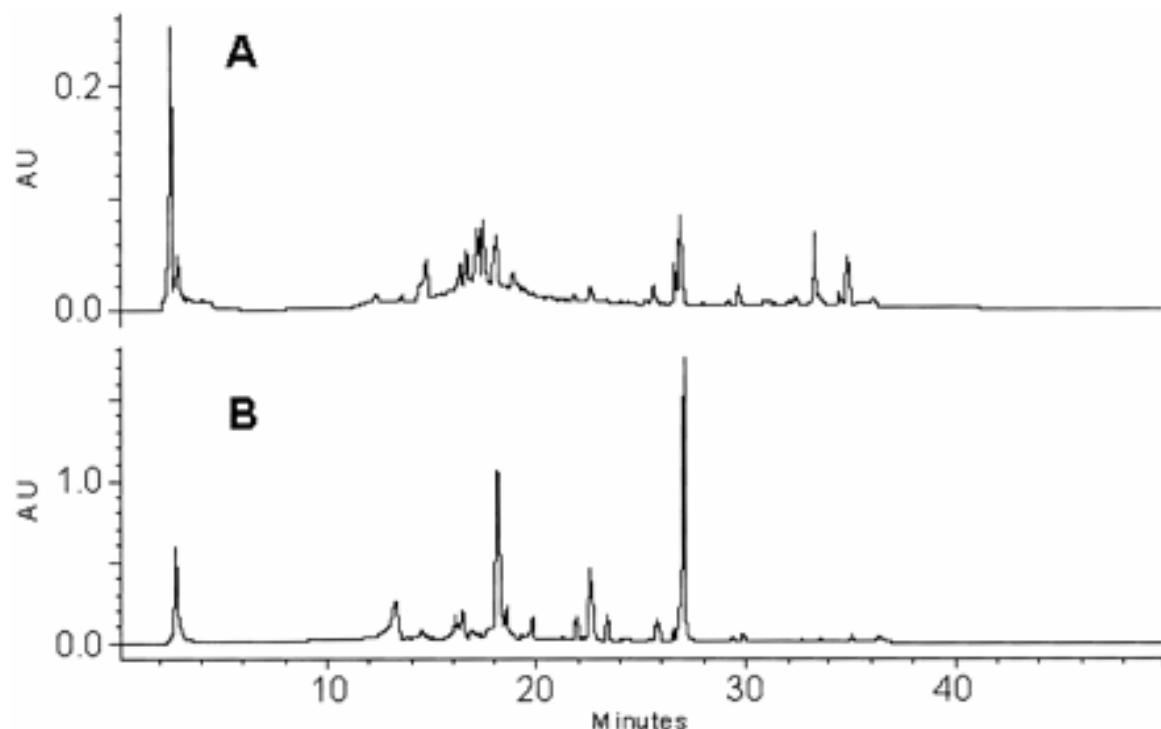


The Safety Evaluation Process

- **History of use and toxicological data**
- **Qualitative versus quantitative differences in product composition over time**
- **Identifying and filling the data gaps**
- **Weight of the evidence safety evaluation**

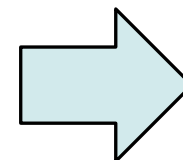
Questions:

- 1) Are lot A & lot B *qualitatively* similar?
- 2) Are lot A & lot B *quantitatively* similar?



Answers:

- 1) Yes.
- 2) No.



Is there a toxicological significance of the differences?

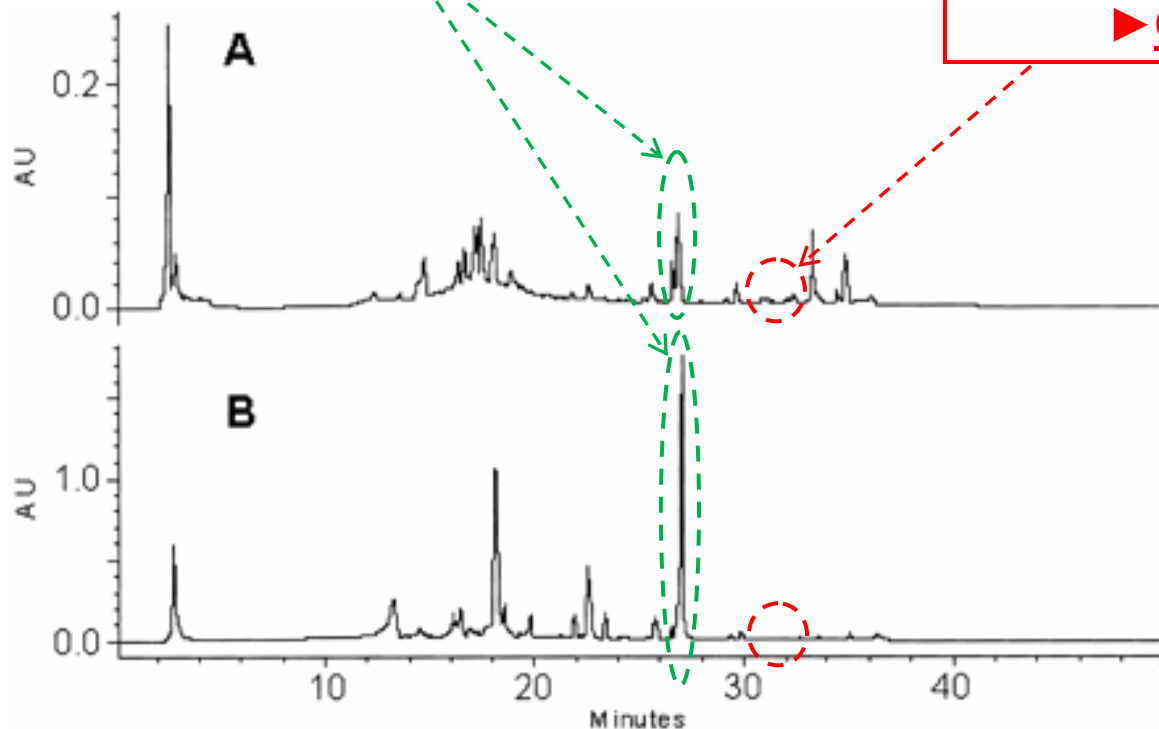
Qualitative and Quantitative Compositional Differences May Be Toxicologically Significant

The EDI may $>$ ADI for B, but not for A.

► Quantitative difference

Even a small amount of a compound of concern can be important.

► Qualitative difference

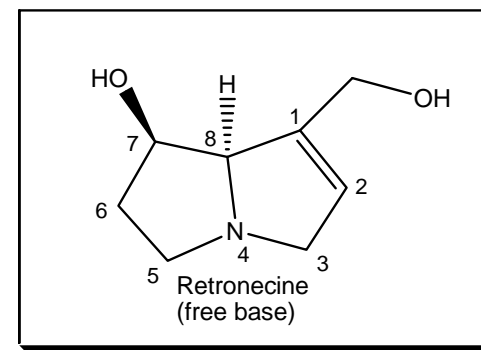
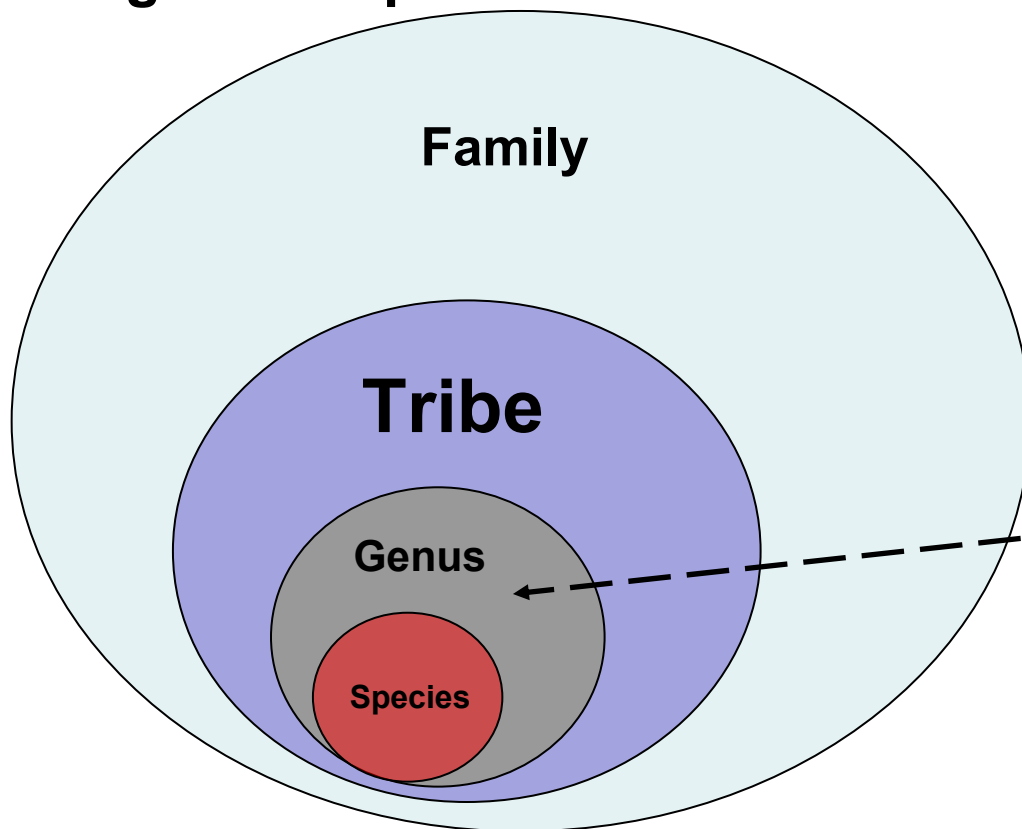


“What else could be in the extract?”

- **Are there (unreported) compounds or classes of compounds of concern present in the extract that we need to look for?**
- **Strategy:**
 - **Use plant taxonomy and correlative phytochemistry as predictive tools to determine possible occurrence**
 - **Perform chemical analyses for key compounds to fill data gaps**

Correlative Phytochemistry Can Help Predict Occurrence of Compounds of Concern

- Research compound occurrence reports for closely related taxa to assess the likelihood of compounds of concern occurring in the species of interest.



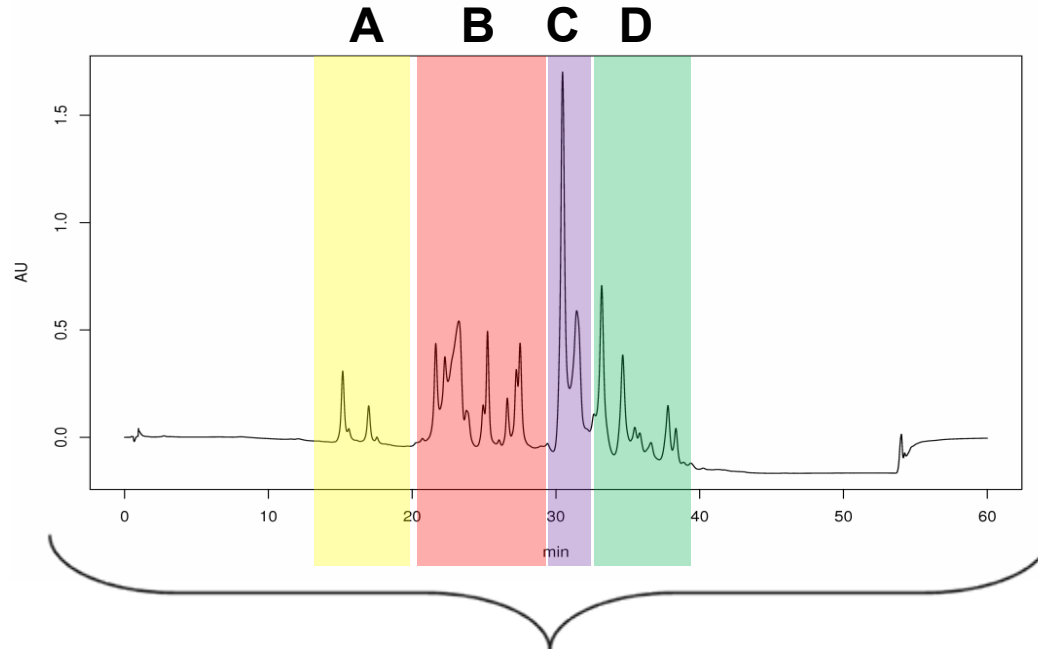
E.g., 1,2-unsaturated pyrrolizidine alkaloids (PAs) occurring in *Symphytum* and *Senecio* spp.

► **Avoid these genera of plants when formulating a botanical supplement, or analyze for PAs.**

Addressing Compounds of Potential Concern

- **If identified compound(s) of concern are not present in the source material or the extract at health-based LOD(s) across an appropriate number of samples, then:**
 - **No specification needed**
- **Set specifications (limits on exposure) as appropriate for chemical classes and/or marker compounds based on:**
 - **Structure/activity relationships (SAR/QSAR)**
 - **Toxicological data**
 - **Historical use/Human exposure**

An extract,
EDI = 2 g/day



Identified
Compounds of
Concern:

V

W

X

Not
Present

Y

Z

Present
Product
Specification
Controls
Level in
Product
(Not to
Exceed ADI)

Chemical Class A

Safe Level
exceeds total
EDI;
Specification Not
Necessary to
control hazard

Chemical Class B

Safe Level
exceeds total EDI;
Specification Not
Necessary to
control hazard

Chemical Class C

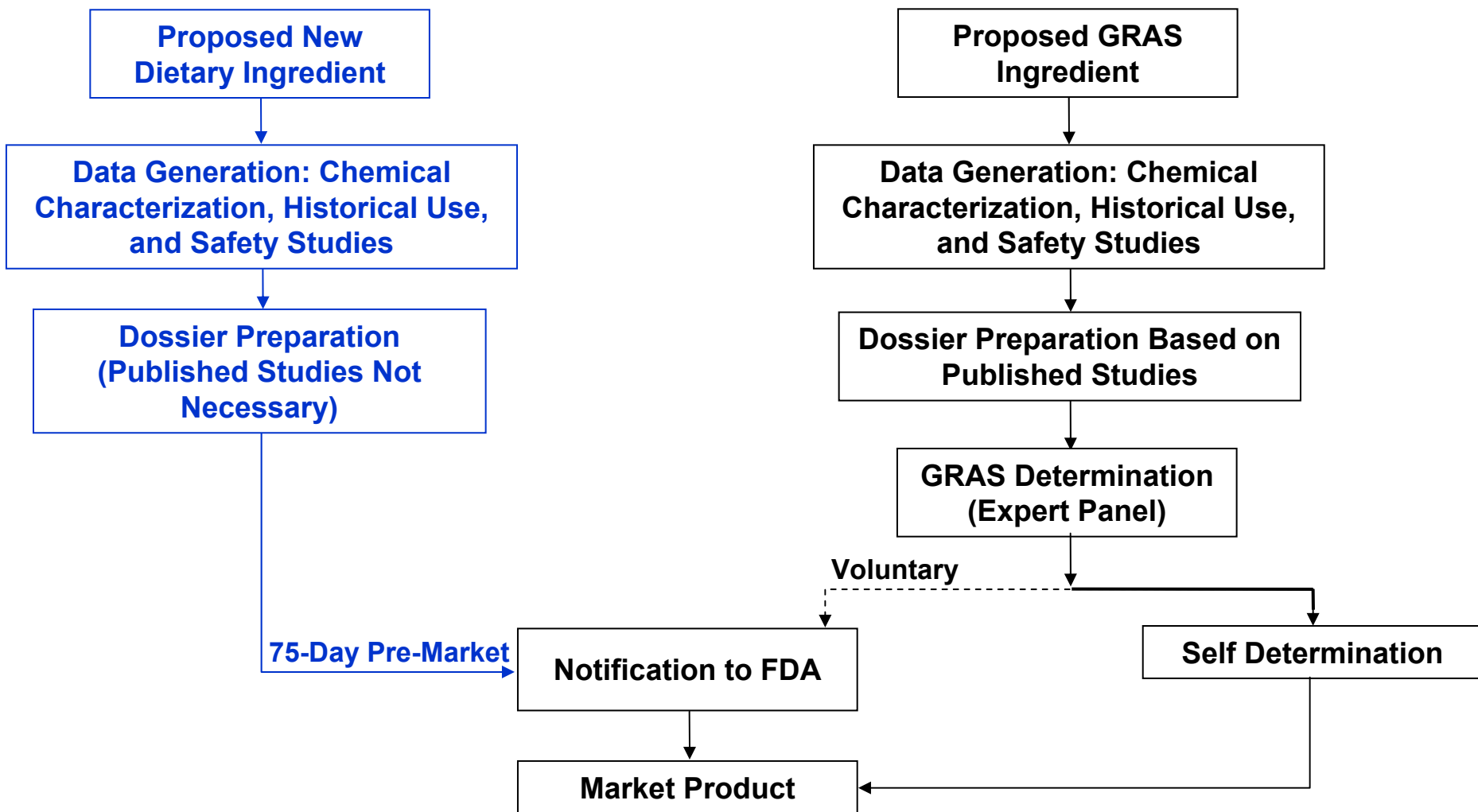
Safe Level
exceeds total EDI;
Specification Not
Necessary to
control hazard

Chemical Class D

Safe Level < 2
g/day
Set
Specifications to
control hazard

- **Identify Hazard**
 - **Bridge to Existing Toxicology Data (Extract, Classes of Compounds, Single Compounds)**
 - **Toxicology Testing**
- **Define Limits of Exposure based on hazard identification**
- **Assess Risk ($EDI < ADI$)**
- **Meet Safety Standard**

Summary of Regulatory Paths



Thank You From the Spherix Team

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 - **A. Wallace Hayes, PhD, DABT**
 - **Nancy Booth, PhD**
 - Ronald Slesinski, PhD, DABT
 - Susan Phillips, MS
 - 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



Thank you!

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