NDI GUIDANCE SEMINAR:
Understanding the New Safety Paradigm

July 26-27, 2011

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Draft Guidance for Industry: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
U.S. Regulatory Paths for New Products

- **Food** Consumed for taste, aroma, nutritive value
  - **GRAS** Intended to become component of or affect characteristics of food
  - **Dietary Supplement** Intended to supplement diet
  - **Drug** Intended to diagnose, cure, mitigate or treat disease
- **Food Additive** Intended to become component of or affect characteristics of food
United States Notifications for New Dietary Ingredients (NDI) for Dietary Supplements (DSHEA)
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
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)
GRAS Process

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 Process

• 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
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
Elements of GRAS Determination

- 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
Elements of GRAS Determination

- **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

<table>
<thead>
<tr>
<th>FOOD ADDITIVE</th>
<th>GRAS</th>
<th>Dietary Supplement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Information and data may be unpublished</td>
<td>Pivotal Information and data must be published</td>
<td>Information and data may be unpublished</td>
</tr>
<tr>
<td>Assumes lifetime exposure</td>
<td>Assumes lifetime exposure</td>
<td>Duration and frequency of exposure dictated on label</td>
</tr>
<tr>
<td>Can not exclude sub-populations</td>
<td>Can not exclude sub-populations</td>
<td>Can target and exclude sub-populations on the label</td>
</tr>
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## Comparison of Regulatory Paths

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

<table>
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<tr>
<th>FOOD ADDITIVE</th>
<th>GRAS</th>
<th>Dietary Supplement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Microorganisms either present or not present in the food supply as an article used for food</td>
<td>Microorganisms either present or not present in the food supply as an article used for food</td>
<td>Only microorganisms present in the food supply as an article used for food</td>
</tr>
<tr>
<td>Synthetic copy of a constituent or extract of an herb or other botanical ingredient (Synthetic duplicates of natural products)</td>
<td>Synthetic copy of a constituent or extract of an herb or other botanical ingredient (Synthetic duplicates of natural products)</td>
<td>Only a constituent extracted from the botanical or extract of an herb or other botanical ingredient (Natural product)</td>
</tr>
</tbody>
</table>
Summary of Regulatory Paths
NDI and GRAS

Proposed New Dietary Ingredient

Data Generation: Chemical Characterization, Historical Use, and Safety Studies

Dossier Preparation (Published Studies Not Necessary)

75-Day Pre-Market

Notification to FDA

Market Product

Proposed GRAS Ingredient

Data Generation: Chemical Characterization, Historical Use, and Safety Studies

Dossier Preparation Based on Published Studies

GRAS Determination (Expert Panel)

Voluntary

Self Determination
NDI or GRAS Ingredients:
Safety evaluation process:
Meeting the safety standard
"I think you should be more explicit here in step two."
Safety Analysis

Bridging to Existing Data

Chemical Characterization

Raw Materials
Processing
Product Specifications

Animal Toxicology

Metabolic Fate

Human Trials

Historical Exposure

Intended Use

Target Population
Intake

Safety Determination
EDI < ADI
Elements of the 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.
Due Diligence Is Necessary

- **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
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

New compounds
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 (Different stability, bioavailability)
New Manufacturing Method and Source Can Change Chemical Composition

<table>
<thead>
<tr>
<th>Process #1</th>
<th>Process #2</th>
</tr>
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<tbody>
<tr>
<td>Ground, dried chicory root</td>
<td>Sucrose from sugar beet or cane sugar</td>
</tr>
<tr>
<td>↓ Isolation, purification</td>
<td>↓ Synthesis (building-up process; forming chemical bonds)</td>
</tr>
<tr>
<td><strong>Inulin</strong></td>
<td>Fructose + Beta-fructofuranosidase from <em>Aspergillus niger</em></td>
</tr>
<tr>
<td><strong>Hydrolysis</strong> (breaking-down process; dissociating chemical bonds)</td>
<td><strong>Short-chain FOS (99% pure)</strong></td>
</tr>
<tr>
<td>Extracellular, thermostable inulinase from <em>Aspergillus fumigatus</em></td>
<td><strong>Short-chain FOS + 10% oligosaccharides</strong></td>
</tr>
</tbody>
</table>
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)

$\geq 95\%$ 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

$\geq 95\%$ Pure compound A
Contaminant Profiles of Naturally-Sourced vs. Synthetically-Produced Pure Compounds Differ

**Isolation from Natural Source**

≥ 95% Pure compound A

Possible contaminants (≤ 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

**De novo synthesis**

≥ 95% Pure compound A

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
Specifications

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

- 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.

\[ \text{Family} \]

\[ \text{Tribe} \]

\[ \text{Genus} \]

\[ \text{Species} \]

\[ \text{Retronecine (free base)} \]

\[ \text{E.g., 1,2-unsaturated pyrrolizidine alkaloids (PAs) occurring in Symphytum and Senecio spp.} \]

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

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

Identified Compounds of Concern:

- V
- W (Not Present)
- X
- Y (Present)
- Z (Product Specification Controls Level in Product (Not to Exceed ADI))
Safety Assessment

- 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
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Thank You From the Spherix Team

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  - Govinder Flora, PhD – Asia
Thank you!

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