

# **Botanical identity, uses, and safety translated to New Dietary Ingredient Notification (NDIN) information**

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# Abstract

As with all subjects, difficulties arise between groups of people who understand the subject from different perspectives. The subject of botanicals is so vast and varied that, while it can be known from one perspective such as in an herbalist's office, the view of the exact same subject matter can be quite different from another perspective, say a regulatory perspective. How does one use botanical knowledge in a regulatory setting? A close view of the NDIN review process can clarify how botanical identity, use, and safety information can be adapted to satisfy regulatory requirements.

# Abstract

How does one use botanical knowledge in a regulatory setting?

# Overview

How does one use botanical knowledge in a regulatory setting?

- Identity of the botanical ingredient
- Ethnobotany/Uses of the botanical ingredient
- Safety of the botanical ingredient

# Botanical Identity

How does one establish identity of a botanical ingredient?







- Collection and/or verification by a botanist
- Voucher specimen
- Characteristic description
- Ecological data
- Intraspecies variation
- Chemical constituents
- Ethnobotanical data



# Botanical Identity

How does one establish identity in a regulatory setting?

## Section 201(ff)(1) [21 U.S.C. 321(ff)(1)]

Defines a Dietary Supplement as:

(ff) The term "dietary supplement"—

(1) means a product (other than tobacco) intended to supplement the diet that bears or contains one or more of the following dietary ingredients:

(A) a vitamin;

(B) a mineral;

(C) an herb or other botanical;

(D) an amino acid;

(E) a dietary substance for use by man to supplement the diet by increasing the total dietary intake; or

(F) a concentrate, metabolite, constituent, extract, or combination of any ingredient described in clause (A), (B), (C), (D), or (E).

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# Botanical Identity

How does one establish identity in a regulatory setting?

- Identity (Description, Composition, Specifications, Serving Forms)
- Identity Verification (NMR, HPLC, HPLC-MS-MS)
- Acceptable ranges for batch-to-batch variability
- Manufacturing (Description, In-Process Controls)
- Identity and levels of any impurities/contaminants
- Description of other ingredients in the supplement

# Botanical Identity

How does one establish identity in a regulatory setting?

Manufacturing and Specifications (see 21 CFR 111.70):

- Describe all points in the process relevant to the safety of the product.
- Include specifications for each component of the dietary supplement.
- Describe analytical methods used to evaluate the specifications.
- Include analytical data when possible.

# Botanical Identity

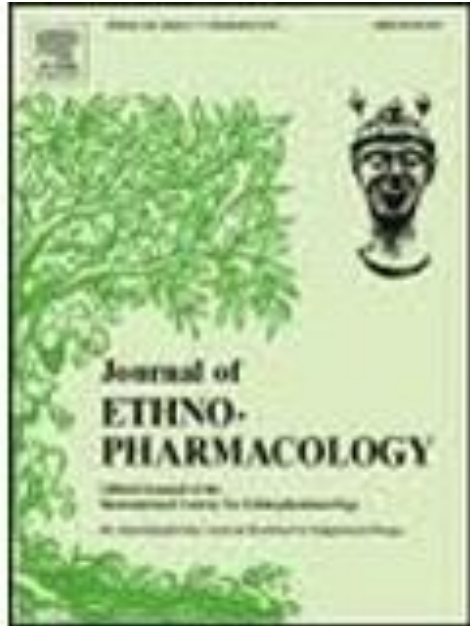
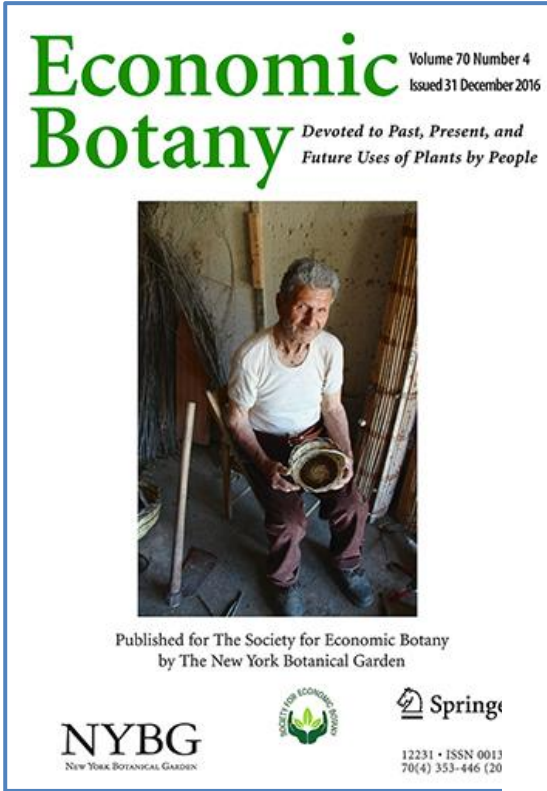
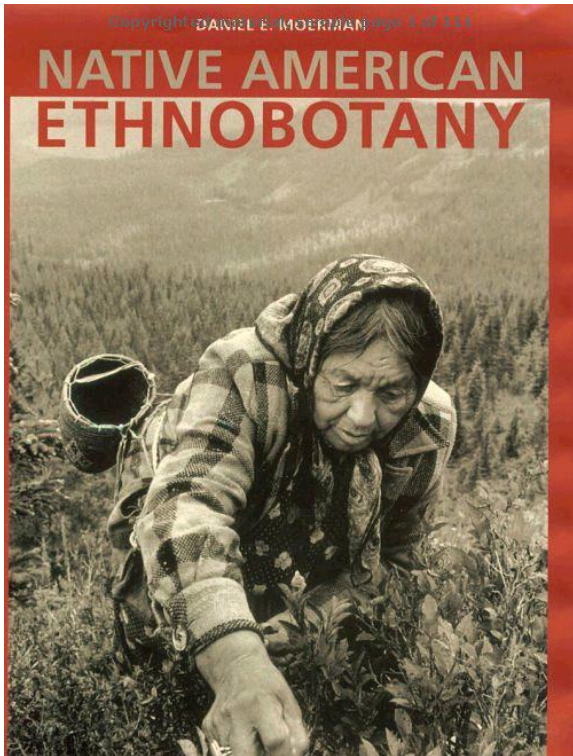
Accurate and detailed identification of botanicals is necessary to inform the review of toxicological/safety data

# Botanical Safety

How does one establish safety of a botanical ingredient?







# Botanical Safety

How does one establish safety of a botanical ingredient?

- Documented traditional consumption
- Currently sizable market presence
- Safety studies or clinical trials have been done
- “I just know”

# Botanical Safety

How does one establish safety in a regulatory setting?

# Botanical Safety

How does one establish safety in a regulatory setting?

## History of Use

- Identity (Description, Composition, Specifications, Serving Forms)
- Ingredient preparation is same or similar to traditional use
- The size and relevant characteristics of the consuming population (e.g., everyone vs. limitations based on age, gender, or health status)
- The number of consumers who used the ingredient
- FDA considers 25 years of widespread use to be the minimum to establish a history of safe use

# Botanical Safety

How does one establish safety in a regulatory setting?

## **Other evidence of safety:**

- Toxicity studies performed on the product of commerce
- Utilizing the same levels as in the product of commerce
- 14-day study to establish a maximum tolerated dose (MTD)
- 90-day sub-chronic oral study to establish an MTD or NOAEL
- A one year chronic toxicity study in an appropriate animal model
- A one-gestation rodent reproductive study
- A repeat-dose tolerability study in humans (30-90 duration)

## Safety testing recommendations matrix

Documented Historical Use	Proposed Use of the NDI		Two-Study Genetic Toxicity Battery <sup>§</sup>	Three-Study Genetic Toxicity Battery <sup>§</sup>	14-Day Range-Finding Oral Study in Animals	90-Day Subchronic Oral Study in Animals <sup>†</sup>	One-Generation Rodent Reproductive Study <sup>†</sup>	Multi-Generation Rodent Reproductive Study <sup>†</sup>	Teratology Study in Animals <sup>†</sup>	One-Year Chronic Toxicity or Two-Year Carcinogenesis	Single-Dose Tolerability and/or ADME Study in	Repeat-Dose Tolerability and/or ADME Study in
Daily Chronic	Intermittent	Less Than Historical Use (see question VI.B.14)	Documented history of use should be sufficient as evidence of safety.									
		Greater Than Historical Use (see question VI.B.19)	✓		✓	✓			✓		✓	
	Daily Chronic	Less Than Historical Use (see question VI.B.14)	Documented history of use should be sufficient as evidence of safety.									
		Greater Than Historical Use (see question VI.B.16)	✓		✓	✓	✓		✓	✓		✓
Intermittent	Intermittent	Less Than Historical Use (see question VI.B.14)	Documented history of use should be sufficient as evidence of safety.									
		Greater Than Historical Use (see question VI.B.18)	✓		✓	✓	✓		✓		✓	
	Daily Chronic	Less Than Historical Use (see question VI.B.15)		✓	✓	✓		✓	✓			
		Greater Than Historical Use (see question VI.B.17)		✓	✓	✓‡		✓	✓	✓‡		✓
No History	Daily Chronic (see question VI.B.20)		✓	✓	✓‡		✓	✓	✓‡		✓	
	Intermittent (see question VI.B.20)		✓	✓	✓‡		✓	✓	✓‡		✓	

# Botanical Identity

- Use established botanical methods for plant ID and document
- Establish acceptance criteria and standards for the ingredient
- Methods and specifications for manufacturing or processing
- Describe correlations between processed and traditional botanical
- Quality control
- Final product/ingredient specifications and testing
- Establish serving size/conditions of use based on traditional use or other use supported by data.

# Botanical Safety

- Established traditional use
- Ethnobotanical data
- History of use compared to serving size and conditions of use
- Appropriate studies chosen based on amount and quality of history of use data
- Appropriate studies chosen based on how the ingredient, serving size, and conditions of use differ from traditional use
- Thorough analysis of study endpoints that are pertinent to activity of the ingredient



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