NEW DIETARY INGREDIENT (NDI) SAFETY INFORMATION

Instructions

- In this template, which supplements the data entry screens in the NDI notification electronic submission portal, you will describe the scientific information on which you base your conclusion that the dietary supplement containing the NDI will reasonably be expected to be safe. Safety information includes, among other things, (1) information showing that the NDI is identical or related to substances documented as having a history of use as food; (2) information showing that the NDI is identical or related to test articles used in safety studies; (3) information showing that a substance or product has a history of use as food; and (4) safety data, including the results of genetic toxicology studies, pharmacokinetic studies, animal toxicology studies and human clinical studies. This template asks for details about the identity of the NDI, verification of that identity, information about history of use as food, and any other evidence relevant to the safety of the NDI under its proposed conditions of use in the dietary supplement. After filling in the template, you will upload the completed template as an attachment to your online NDI notification and attach files containing the scientific publications cited in your notification.

- For a notification that concerns the use of an NDI in a dietary supplement that contains no other ingredients, the safety of the NDI and the dietary supplement would be synonymous.
In other situations, however, that may not be the case. For example, when an NDI is used in a dietary supplement with one or more other NDIs, the safety of the dietary supplement may not be the sum of the safety of the individual NDIs. In such circumstances, you should document your basis for concluding that the dietary supplement will reasonably be expected to be safe and explain why that conclusion is reasonable. For example, if two botanical extracts have separate histories of use in traditional medicine, but no history of being used together, the safety of the combination may not be clear from the safety information pertaining to the individual NDIs. On the other hand, if an extract of a medicinal herb is combined with an extract of a material that has a long history of safe use as food, then it may be reasonable to conclude that the combination is safe based on information about the safety of the individual NDIs. If you wish to submit a notification for the use of an NDI in a dietary supplement with other NDIs, the FDA recommends that you confer with a member of the New Dietary Ingredient Review Team in FDA's Division of Dietary Supplement Programs about how to proceed. If you have any questions concerning this matter, please contact the New Dietary Ingredients Review Team by email at NDITEAM@fda.hhs.gov.

- If a section or subsection is not applicable to your notification, mark "N/A" in your response.

- Sections marked as "Required" in the template's section headings must have complete responses in all subsections for which you have data. If you leave a "Required" section blank or respond "N/A," FDA will consider your notification incomplete for failure to

comply with 21 CFR 190.6(b). An incomplete notification does not satisfy the requirement to submit an NDI notification. You may not introduce your NDI or a dietary supplement containing the NDI into interstate commerce, or deliver the NDI or dietary supplement for introduction into interstate commerce, until at least 75 days after you have submitted a complete notification to FDA.

- Please include full citations for all published and unpublished sources cited or relied on in your notification in the Reference List (Section 5). You will be prompted to attach e-copies of these sources when you return to the electronic submission portal after filling in this template.

- The template includes some sections identified as "Recommended." These sections solicit information that FDA considers helpful in evaluating NDI notifications. You are encouraged but not required to respond to template sections that are identified as "Recommended." However, if you leave a "Recommended" section blank or respond "N/A" and FDA determines that the information is needed to establish safety, your notification may be considered inadequate to conclude that the NDI will reasonably be expected to be safe under its proposed conditions of use in the dietary supplement.

Table of Contents

1. New Dietary Ingredient Identity Information (Recommended)

1.1 Description of the identity of the NDI

Vernonanthura nudiflora hydroethanolic extract

1.2 Description of the evidence verifying the identity of the NDI

Presence of Identificatory molecule in the NDI

1.3 NDI manufacture

(b) (4)

Please note*: In a typical NDI notification, the description of the NDI's manufacture contains trade secrets (TS) and/or confidential commercial information (CCI). You may indicate to FDA your designation of information as TS or CCI in Section 2 of the NDI portal. You also may indicate in that section whether you are attaching a redacted copy of some or all of the notification. If you provide a redacted copy of the notification or a list of information that you believe to be TS or CCI, you should upload and attach it in Section 5 of the NDI portal.*

1.3.1 Raw materials

(b) (4)

1.3.2 Formulation ingredients

(b) (4)

1.3.3 Manufacturing process

(b) (4)

1.3.4 NDI specifications

(b) (4)

(b) (4)

1.1.1 Disintegration and Methods of analysis

Parameters analyzed according to USP

TLC or HPLC for (b) (4) identification

1.1.2 Analysis of potentially toxic processes

(b) (4)

1.1.3 Dissolution profile

N/A

1.1.4 Shelf-life and conditions of storage

1.5 years in well closed container, away from humidity, heat and direct solar light

2. Dietary Supplement Manufacture (Recommended)

2.1. Raw materials

(b) (4)

2.2. Formulation ingredients other than the NDI

(b) (4)

2.3. Manufacturing process

(b) (4)

2.4. Product specifications

(b) (4)

2.5. Methods of analysis

Methodologies according to USP

2.6. Analysis of potentiallytoxic processes

(b) (4)

(b) (4)

2.7. Disintegration and dissolution profile

N/A

2.8. Shelf-life and conditions of storage

1.5 years in well closed container, away from humidity, heat and direct solar light

3. History Of Use Or Other Evidence Of Safety (Required)

3.1 History of use

3.1.1 Description of the relationship between the historically consumed material and the NDI or dietary supplement containing the NDI

Vernonanthura nudiflora has been used as an infusion by part of rural people in Uruguay

3.1.2 Describe identity information verifying the relationship between the historically consumed material and the NDI or dietary supplement containing the NDI

NDI is an herb extract from the same plant that has been used by rural people as an infusion

3.1.3 Historical conditions of use and cumulative exposure estimate for the historically consumed material

Used as an infusion by rural people during their lives

3.1.4 Adverse events associated with historically consumed material

No record of adverse events

3.1.5 Alternative rationale for reasonable expectation of safety based on history of use

Herb grows naturally in the country and animals occasionally consume it without adverse effects registered

3.2 Other evidence of safety

3.2.1 Safety study type

Toxicity test in mice

3.2.2 Safety study title, if any

Acute Systemic Toxicity via Oral gavage in CD-1 Mice, Repeat Dose

3.2.3 Citation for the safety study (either public or non-public), if any

Non public study, Reference code (b) (4)

Toxicity study performed in compliance with the United States Food and

Drug Administration (FDA) Good Laboratory Practice (GLP) for Nonclinical Laboratory Studies, Title 21 of the U.S. Code of Federal Regulations, Part 58.

3.2.4 Identity information verifying the relationship between the test article and the NDI or the dietary supplement

Toxicity study was performed with the same herb extract presented as New Dietary ingredient

3.2.5 Route of administration, serving size, frequency of use, interval between servings, and duration of use of the test article

Oral gavage

Dose 0.1ml daily for mice weighting approx. 20g

14 days study

3.2.6 Study design and safety metrics

(b) (4)

(b) (4)

3.2.7 Discussion of toxicity and conclusion

(b) (4)

3.2.8 Alternative rationale for reasonable expectation of safety based on other evidence of safety

(b) (4)

4. Basis For Concluding That the New Dietary Ingredient Will Reasonably Be Expected To Be Safe For Use in the Dietary Supplement (Required)

(You must either provide the information requested in Subsections 4.1 to 4.6, when applicable, or explain in Subsection 4.7 your alternative rationale for concluding, based on the totality of the scientific evidence, that the NDI will reasonably be expected to be safe under its proposed conditions of use in the dietary supplement.)

4.1 Determination of the No-Observed-Adverse-Effect-Level (NOAEL) or Lowest-Observed Adverse Effect Level (LOAEL)

4.2 Determination of safety factor

4.3 Determination of the Acceptable Daily Intake (ADI)

4.4 Determination of Estimated Daily Intake (EDI) and the EDI/ADI Ratio

4.5 Determination of margin of safety

4.6 Safety narrative and conclusion

4.7 Alternative basis for reasonable expectation of safety

Presented NDI is a hydroethanolic extract from a natural herb

Four different approaches have been taken in order to determine consumption safety

Toxicity study on presented NDI executed by a registered laboratory and performed in compliance with the United States Food and Drug Administration (FDA) Good Laboratory

Practice (GLP) for Nonclinical Laboratory Studies, Title 21 of the U.S. Code of Federal Regulations, Part 58

Result of this showed no toxicity evidence from NDI

Microbiological analysis showing no presence of pathogens in the NDI

History of use of the herb by rural people in Uruguay without records of adverse effects, complemented by occasionally ingestion of the herb by animals without any case of toxicity registered

(b) (4)

Given mentioned evidenced, we conclude that there is reasonable evidence to corroborate presented NDI's safety of consumption

5. Reference List (Required)

Documents supporting our presentation

1. *Toxicity study in mice*
2. *Microbiological analysis*
3. *Letter from Uruguayan chamber of phytomedicines*
4. *Study performed in cell cultures*

6. Comments

(You have the option to provide any additional information about the NDI or the dietary supplement that you believe will assist FDA in processing your notification.)