A Critique of the Standardized Information on Dietary Ingredients Protocol, Part II

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Editor's Note: *This is the second of a 2-part article. The first part ran in the last issue, Feb-Mar 2010 (*IMCJ. *2010;9.1:34-37).*

As I wrote about last issue, the Standardized Information on Dietary Ingredients (SIDI) protocol was developed by the Standardized Ingredient Information Protocol (SIIP) Working Group, a joint trade association effort with participants representing both dietary supplement (DS) ingredient suppliers and finished product manufacturers. Members include the Council for Responsible Nutrition, the American Herbal Products Association, the Natural Products Association, and the Consumer Healthcare Products Association.

The objective of the working group is to develop standardized guidelines and protocols that suppliers of vitamins, minerals, botanicals, and other dietary ingredients can voluntarily use to help convey relevant and required information to finished product manufacturers who make capsules, tablets, liquids, etc, from these raw ingredients. The guidelines are intended to be both comprehensive and flexible so as to apply across all product categories. The reason for the guidelines is to address the prevailing need for communicating information in a standardized manner, effectively reducing paperwork and resources currently dedicated to this process.

The SIDI program achieves 3 main functions:

1. It integrates information on raw sourcing for dietary ingredients (from suppliers or their brokers and/or distributors; hereinafter just referred to as suppliers) into several voluntary, standardized forms (templates), thereby eliminating the need for each manufacturer to have its own questionnaire to certify a supplier;
2. through these templates, the program defines the minimum type and scope of information that should be covered; and
3. the templates provide a forum for suppliers to develop their own dietary ingredient data sheets (DIDS) to be sent to manufactures in lieu of answering disparate questionnaires from each manufacturer.

The working group developed 3 templates: Botanical Materials, Non-Botanical Materials, and a Site Quality Overview Data Sheet.

Without question, SIDI's goals are both much needed and well intentioned. But, as I delved into last issue, I do see some program shortfalls. In this issue, I would like to examine the actual example that the SIIP Working Group asks suppliers to follow.

A Critique of the SIIP Working Group's Sample Botanical Template

The SIIP Working Group provides a completed template to serve as an example of how the form should be filled out (to see the whole example, go to www.ahpa.org/SIDI/PDFs/09-13GLISODINform-SIIPlr.pdf; for your convenience, to view a reproduction of just the parts discussed in this article, see pp 48-50).

Though I can appreciate the intent, when I examined and studied all of the information provided in the example, I found that critical information was not included. This does not set a very good precedent, as an incomplete example may send a less-than-desirable message to all who look to follow it.

Following are my comments on inadequacies in the given example of GliSODin powder/*Cucumis melo*:

Section 2: Although the asterisk below Section 2 asks for botanical identification to be given in the "AGRICULTURAL PROCESS" box, in this example, no identification method is provided to verify genus and species of the fruit (genus/species is listed in Section 3 under "LATIN BINOMIAL," but no method of identification is given there either).

In addition, the raw material specification sheet provided (see "SPECIFICATIONS FOR GLISODIN 1.0 IU/MG POWDER," p 50) also shows no identity parameter for the fruit.

Section 2, GMP COMPLIANCE: The form says "GMP Certification attached," but no such certification is included in the documentation.

Section 2, STERILIZATION or FUMIGATION METHODS: What does the answer "N/A" (ie, not applicable) mean, exactly? This is especially confusing because on the aforementioned spec sheet, "SPECIFICATIONS FOR GLISODIN 1.0 IU/MG POWDER," there is a listing and values are given for microbial counts. With this being the case, how does N/A apply?

Section 2, KNOWN or POTENTIAL IMPURITIES (including solvents): This is left blank. Why? Once again, an explanation is warranted because the spec sheet lists pesticide residues.

Section 3, INGREDIENT LIST (include excipients): Kudos to SIDI for adding an ingredient list that includes excipients and weight percentages, but, in this example, weight percentage is left unspecified. In my own experience, ingredient percentages are something I often have to chase down, and to have this filled out

is helpful. An example is buying deglycyrrhized licorice, where 1 company may put in 70% maltodextrin and another company offers the product with no excipients whatsoever. Its pretty obvious what is the more appealing product—but I would prefer the information be provided

Section 3, CONTROL of IMPURITIES & LOT-to-LOT VARIATION: Although the second half of this equation, lot-to-lot variation, is answered in that "SOD activity is certified each batch according to the validated test method" (and the test method is given in an accompanying document, not shown here), the control of impurities is not addressed. Once again, the spec sheet lists both pesticide residues and microbial counts, so impurities do exist.

Section 3, OTHER: Requested in this section is the applicable bioassay method. However, no method is given (it is just stated that the method is "available on request.") This leaves a potential hole, as, without knowing the bioassay method, you have no way to assess material purity or strength. It is good that they will "send upon request," but, in terms of this completed form, an important piece of information has been left out.

Let me make it clear here that I am not simply fussing over details. As I've mentioned in both Parts I and II of this article, the reason for these guidelines is to develop standardized guidelines and to address the prevailing need for communicating information in a standardized manner, effectively reducing paperwork and resources currently dedicated to this process.

If you have to go back to the company to get information that is essential to judging the quality of the ingredient, the "standardized guidelines" have been compromised (what is the point of having a guideline if the answer is not provided on the information you are given) and a major element of "reducing paperwork and resources" has been lost.

It's not that the response is bad in and of itself; it's just that by excluding the information, you have created additional work—which this form is intended to reduce.

As a final consideration, you need to realize that some companies will intentionally leave out information such as this to hide poor quality. They also may not include it because such information is proprietary. In this latter case, it is generally sufficient to ask for a confidentiality agreement.

Section 6, SUGGESTED PRODUCT CLAIMS: Dosage is requested but in the example response, none is given. It is critical to list the dose range for a raw material because the upper recommended dose needs to be known in order to calculate and approximate the acceptable parts per million levels of heavy metals and solvent residue—the permitted daily exposures in mg/d levels.

Comments on What the Templates Are Missing

As well as the shortcomings listed above, following are my thoughts on what I believe that the templates should have but that are missing or inadequate:

The templates should not be changeable. If a requested piece of information is N/A, it can be noted as such, but it should remain on the template for those times when it is not N/A. If more information is needed because the template does not address a certain area, then there should be a section where this can be added. Point being, by keeping the basic template structure the same, the consistency and integrity of the template are both maintained.

The Botanical Materials and Non-Botanical Materials templates should specifically mimic what GMP regulations require in regard to identity verification (they do not). Ideally, these templates should have a specific line item for identity (as mentioned above, the asterisk below Section 2 asks for botanical identification to be given in the "AGRICULTURAL PROCESS" on the botanical template and it is not even mentioned on the nonbotanical template). Since the US Food and Drug Administration (FDA) mandates that identity testing/examinations be conducted on every batch received, it certainly warrants its own line on the template.

Neither template gives specifics as to which impurities/contaminants should be considered or declared in relation to the product being reported. This is a very serious omission. The form should require the supplier always to address the following items, as applicable (that is not to say randomly, please read the footnote).[a] bacteria, yeast, and mold profiles; aflatoxins (at least B1, B2, G1, and G2); solvents used; heavy metals; herbicides; and pesticides. If the ingredient is an oil, it should include rancidity markers. If these are listed on the certificate of analysis (COA) or a spec sheet provided with the lot, that can be noted.

To do this, each supplier needs to be forthcoming with information so that a manufacturer doesn't have to call and query with individual questions. In short, for this form to be really valuable, it has to be comprehensive, and this question is one of the most crucial of all to ask when it comes to quality.

A specific and stand-alone line item for the bioassay method used for strength verification should be 1 of the unchangeable items on the template. This is actually a case in point why the template should be inalterable: On the original template, "BIOASSAY" does have its own line, but in the example given here, this has been morphed under "OTHER" (Section 3), thereby diminishing its importance.[b]

It is also essential that this parameter (bioassay method used for strength verification) ask for the type of standard used to verify the assay: Primary, Secondary, In House, or Reagent Grade. (For a detailed explanation of these grades, please see *IMCJ*. 2005;5.1:34-37) The reason for this is that all ingredients have to be compared to a known standard. For example, kava (*Piper methysticum*) is graded for its kavalactones. Depending on what standard is used, there will be variable answers, so it is obviously important information.

Neither the botanical nor nonbotanical template asks if the assay result reported is on a "dry" or "as is" basis (ie, including whatever the ambient moisture is): It should. Typically,

[a]The statement "as applicable" does not mean randomly. Certain products do not need all the tests—vitamin powders, for example, do not need an aflatoxin or pesticide panel, whereas herbs and other botanicals do.

[b]The original template is not shown here. To see a template that is not filled in—hence unaltered—see www.ahpa.org/SIDI/documents.html and click "Template for Botanicals (MS Word)."

PRODUCT INFORMATION DATASHEET
Botanical Dietary Ingredients

GliSODin
The Antioxidant Catalyst™

Section 1 - BOTANICAL INGREDIENT IDENTITY AND COMPOSITION	
PRODUCT NAME & CODE:	GLISODIN ® 1 IU/MG POWDER
COMMON or USUAL NAME of BOTANICAL:	Superoxide Dismutase/Gliadin Complex
SCOPE of DOCUMENT:	Sample Document for Presentation Purposes Only
GENERAL PRODUCT INFORMATION:	Cucumin melo (melon) extract, standardized to Superoxide Dismutase content, combined with Gliadin.

Section 2 - BOTANICAL MANUFACTURING INFORMATION	
NAME & ADDRESS of MANUFACTURING SITE:	Isocell Nutra/53 blvd du General Martial Valin, Paris 75015 France
RELATIONSHIP to MANUFACTURER:	PL Thomas is the exclusive Distributor for North America
AGRICULTURAL PROCESS*:	Traditional cultivation of Cucumin melo fruits
MANUFACTURING PROCESS:	Flow chart attached
GMP COMPLIANCE:	GMP Certificate attached
STERILIZATION or FUMIGATION METHOD(S):	N/A
KNOWN or POTENTIAL IMPURITIES (including solvents):	

* Include method(s) of cultivation (Ex: sustainably-wildcrafted, or cultivation method), identification, harvest, handling, & post-harvest processing.

Section 3 - SPECIFICATIONS

INGREDIENT LIST (include excipients):

COMMON or USUAL NAME (per current Herbs of Commerce):	**LATIN BINOMIAL:**	**PLANT PART USED:**	**ORIGIN*:**	**HARVEST AGE/ SEASON:**	**CAS #:**	**WEIGHT PERCENT:**
Melon SOD (EXTRAMEL ®)	Cucumis melo	Fruit	France			XX%
Gliadin, extracted from wheat (GLIAMINE ™)		Wheat Protein	France		9007-90-3	XX%
Maltodextrine, produced by hydrolysis of wheat starch (GLUCIDEX 12W)		Wheat starch	France		9050-36-6	XX%

CURRENT PRODUCT SPECIFICATION SHEET ATTACHED:	Specification sheet attached
CONTROL of IMPURITIES & LOT-to-LOT VARIATION:	SOD activity is certified each batch according to the validated test method.
OTHER (including bioassay method if applicable):	Assay method available on request

* For botanicals specify country-of-origin; for excipients specify source information (synthetic, animal, vegetable, mineral, fermentation, etc.).

Section 4 - LABELING INFORMATION	
NUTRITION/SUPPLEMENT FACTS LABELING (including nutritional profile):	Nutritional Profile attached
REQUIRED FINISHED PRODUCT LABEL STATEMENTS:	1. The GliSODin logo must be prominently displayed on the label 2. Recommended labeling for supplement facts: Superoxide Dismutase/Gliadin Complex ...xx IU (SOD activity) 3. Additionally, maltodextrin should be included in the "Other Ingredients" section 4. Wheat warning – "Caution: Do not take this product if you are allergic to wheat or gluten." 5. Patent & Trademark notation: "Isocell SA, France is the owner of US Patent Nos. 6,045,809 and 6,426,068B1 and trademark for GliSODin®"
RECOMMENDED RESTRICTIONS of USE:	"Caution: Do not take this product if you are allergic to wheat or gluten."

Section 5 - REGULATORY INFORMATION	
PATENT COVERAGE:	US 6,045,809 / US 6,426,068
COMPENDIAL GRADE:	
REGULATORY STATUS (include supporting documents):	Freely sold in USA under DSHEA
PRODUCT MASTER FILE(S):	Upon request
BSE/ TSE INFORMATION:	BSE statement attached
VEGAN or VEGETARIAN STATUS:	Vegetarian product
ALLERGENS/ HYPERSENSITIVITES:	Product contains Gliadin – a wheat derivative. See Required Labeling (Section 4).
SORBATES and/ or SULFITES:	N/A
KOSHER/ HALAL STATUS*:	N/A
ORGANIC STATUS*:	N/A
GMO STATUS (for each natural ingredient):	NON-GMO statement attached
TARIFF CODE for IMPORT or EXPORT:	HTS#1302.19.40.40
*Include certifying agency/authority	

Section 6 - MISCELLANEOUS PRODUCT INFORMATION	
BATCH/ LOT NUMBERING SYSTEM:	YEAR / DAY / FACTORY CODE
BATCH DEFINITION:	06/254/C274 (06 for 2006 and 254 for the 11 September)
EXPIRATION DATING:	Shelf life 24 months from date of production
RECOMMENDED STORAGE CONDITIONS:	Between 5 and 20° C in a dry place in non open commercial packaging
OTHER OPTIONAL INFORMATION:	
PACKAGE SIZE OPTIONS:	Net weight: 10kg drum – inner package: double polyethylene 90µm bags and one desiccant sachet (10x10) between double bags. Outer package: 34L white drum made of high density polyethylene. Closure: Red plastic cover.
SUGGESTED PRODUCT CLAIMS (including supporting documentation & dosage):	The following Structure / Function claims have been submitted to FDA: - Promotes the production of the body's own, natural antioxidants. - Clinically proven to help maintain cellular health and protect against damage caused by oxidative stress. - Reduces lactic acid build up in humans under physical stress. - Supports Healthy Immune Function. - GliSODin is an antioxidant catalyst. - Supports skin health against photo-oxidative stress
MSDS (attach):	MSDS attached

Section 7 - REVISIONS			
REVISION DATE:	13 September	REVISION LEVEL:	1

Section 8 - CONTACT INFORMATION			
COMPANY NAME:	P.L. Thomas & Co., Inc, 119 Headquarters Plaza, Morristown, NJ 07960		
CONTACT NAME:	Scott Rosenbush	TITLE:	Botanical Business Manager
CONTACT PHONE:	973-984-0900 ext 223	EMAIL:	scott@plthomas.com

ISOCELL

NUTRA
SPECIFICATIONS OF GLISODIN® 1IU/MG POWDER

Article N° ISON.A001.H

Test item	Specifications	Reference / Analytical Procedure
1. Appearance	White to beige dry powder with a melon characteristic odor	European Pharmacopoeia 6th
Tests		
2. Particle size	90% w/w < 200 µm	Internal monograph
3. Loss on drying	≤ 7%[1]	European Pharmacopoeia 6th
4. Ash	<0.5% on dry[1]	European Pharmacopoeia 6th
5. Carbohydrate	94 to 98% on dry[1]	European Pharmacopoeia 6th
6. Lipids	<0.5% on dry[1]	European Pharmacopoeia 6th
7. Protein	2 to 6% on dry[1]	European Pharmacopoeia 6th
Heavy metals		
8. Lead	<3 ppm	European Pharmacopoeia 6th
9. Cadmium	<1 ppm	European Pharmacopoeia 6th
10. Mercury	<0,1 ppm	European Pharmacopoeia 6th
11. Arsenic	<2 ppm	European Pharmacopoeia 6th
Pesticide residues[2]		
12. Organochlorine	According to the EP6th	European Pharmacopoeia 6th
13. Organophosphorus	According to the EP6th	European Pharmacopoeia 6th
Residual solvents		
14. Ethanol	<4%	European Pharmacopoeia 6th
15. Other solvents	None	European Pharmacopoeia 6th
Assay		
16. SOD	≥1 IU NBT[3] /mg	Internal monograph N°50
Microbial tests		
17. Total flora	<1000 CFU/g	European Pharmacopoeia 6th
18. Yeast and Mould	<100 CFU/g	European Pharmacopoeia 6th
19. Enterobacteriae and other gram-negative bacteria	<100 CFU/g	European Pharmacopoeia 6th
20. E. coli	Not detected /1g	European Pharmacopoeia 6th
21. Salmonella	Not detected /10g	European Pharmacopoeia 6th
22. Staphylococcus aureus	Not detected /1g	European Pharmacopoeia 6th

Dr. Anne-Laure CAMARA — May 5th, 2009
Director of Development and Quality Assurance

[1] Not mandatory specification: Manufacturing follow-up
[2] Frequency: 2/year (set up in 2009)
[3] 1 IU NBT corresponds to the melon extract quantity inhibiting 50% of NitroBlue Tetrazolium (NBT) reduction.

raw material arrives with some level of moisture content (1%-10% is possible), so if the assay data reported on the template is on a "dry basis," the DS manufacturer already knows its own real-world testing will not meet what the supplier states. Why? Because a shipped product will rarely, if ever, remain dry—every material has its own range of water absorption and some are more or less hydrophilic (they absorb more/less moisture from the air) than others.

With this in mind, let's say the moisture content equals 10% (ie, 10% of the product is water), and a company claims a product strength of 98%. We know that is mathematically impossible—the best you could get is 90%, and even that is not generally possible because there are usually other constituents.

Neither template asks for a COA to go with a specific lot number. I believe this is essential so that it is ensured the supplier's template provides what the FDA GMP regulations allude to in 111.75 (B): "The certificate of analysis includes a description of the test or examination method(s) used, limits of the test or examinations, and actual results of the tests or examinations."[1] Neither template includes a physical description requirement. It should, especially if buying whole plant material, but also for other types of ingredients. For example, I buy powders, and I need to know if the powder should be a deep brown or a more yellow brown. A physical description is the first rung on the quality assurance ladder.

Both templates should include a specific line item requesting that, if any stability testing has been performed, the data be available for examination—again, a very important piece of information to know if I'm putting this in a DS that will sit on a shelf for months.

If any of the items I have listed here might be included in the specification sheet or the COA that would be provided by the supplier, then the SIDI protocol should specify exactly what mandatory information each of those documents should contain to make sure it is given somewhere and can be referenced by the buyer.

The intent of the SIDI protocol is clearly positive and of significant value for DS manufacturers. I suggest that the templates need a more detailed structure (and one that is only variable in additions but not subtractions from the form), which would help to address the various concerns listed in my 2 articles.

Rick Liva, ND, RPh, graduated from Temple University School of Pharmacy in 1975 and National College of Naturopathic Medicine in 1982. He is the managing physician at the Connecticut Center for Health, located in Middletown and West Hartford. Dr Liva is a founding member of the American Association of Naturopathic Physicians and past president of the Connecticut Society of Naturopathic Physicians. As mentioned in the disclosure, he is also the president, CEO, and director of Quality Control and Quality Assurance at Vital Nutrients, a company certified by the Natural Products Association for current Good Manufacturing Practices.

Reference

1. Department of Health and Human Services. US Food and Drug Administration. §111.75 What must you do to determine whether specifications are met? *Current Good Manufacturing Practice in Manufacturing, Packaging, Labeling, or Holding Operations for Dietary Supplements: Final Rule.* College Park, MD: Food and Drug Administration; 2007:773.