AOAC/NIH-ODS 5-YEAR PROJECT RESULTS IN 34 SMPRS AND 16 *OFFICIAL METHODS*℠ FOR DIETARY SUPPLEMENT INGREDIENTS

In September 2018, AOAC successfully completed a 5-year contract with the U.S. National Institutes of Health-Office of Dietary Supplements (NIH/ODS) to establish voluntary consensus standards for 25 high-priority ingredients, with the goal of *Official Methods*℠. The project resulted in 34 *Standard Method Performance Requirements* (SMPRs®) and 16 *Official Methods*℠ for priority dietary supplement ingredients that reflect the needs of the dietary supplements community (*see* SPDS Standards and Methods in Process: Status of Ingredients at a Glance on page 21 of this issue). ››

AOAC/NIH-ODS 5-Year Project Results in 34 SMPRs and 16 *Official Methods*℠ for Dietary Supplement Ingredients

Darryl Sullivan, Eurofins Food Integrity and Innovation and Chair of SPDS since its inception in 2014

"Many of our members and staff consider this one of the largest, most challenging, and successful projects in AOAC's history," said Executive Director **David B. Schmidt.** "AOAC's work in the dietary supplements area has resulted in an impressive list of standards developed and methods adopted. Yet, there is an opportunity to expand upon this seminal work to provide further analytical solutions for the dietary supplements industry, working in collaboration with NIH and AOAC. We are seeking stakeholder input on this at the Midyear Meeting."

Critical to the success of the project was engagement of industry representatives participating on the advisory panel, stakeholder panel, working groups, and expert review panels (ERPs) to ensure that efforts are relevant, timely, and meet the needs of stakeholders.

"Support from industry stakeholders was important to work together to set standards and find the best methods," said **Darryl Sullivan** of Eurofins Food Integrity and Innovation and chair of the AOAC Stakeholder Panel on Dietary Supplements (SPDS). "Not having standards in place impacted companies that pride themselves on quality because they have to compete with every company out there whose products may not meet label claims. AOAC standards and methods helped level the playing field for the dietary supplements industry."

The analysis of complex dietary supplements poses many challenges. Dietary supplements are often mixtures of large numbers of compounds. Further, compounds of dietary supplements are often unstable, making extraction difficult and posing reference material challenges. Methods are needed with analytical ranges appropriate to everything from raw materials to finished products. There is a lack of uniform industry test standards necessary to help resolve safety, quality, and regulatory issues that follow as a result. Standardized methods are urgently needed.

AOAC leveraged networks and dietary supplements stakeholders for industry outreach and engagement to develop voluntary consensus SMPRs and modernize methods. AOAC rallied industry to participate to drive the effort and ensure that the work is relevant.

The overall objectives of the contract were to provide ODS with "a stakeholder-informed master list of dietary supplement ingredients/finished products for which scientifically valid methods are lacking; to use a formal process to set stakeholder-informed priorities for the order in which method needs identified in the master list will be addressed; and to provide consensus driven expert guidance in selecting individual high-priority methods to become candidate methods for future validation studies."

Since the contract signing in September 2013, AOAC facilitated:

- Six advisory panel meetings to identify key stakeholders, subject matter experts, issues, and ingredients, and set priorities for the stakeholder panel. The panel identified and prioritized 25 dietary supplement ingredients for which systematically reviewed analytical methods are needed.
- Ten stakeholder panel meetings to examine voluntary consensus standards for possible adoption. SMPRs were adopted for all 25 priority ingredients, some of which required more than one standard.
- Twenty-five working groups to develop and recommend SMPRs that meet the needs of stakeholders for each priority dietary supplement ingredient
- Seven ERPs to evaluate candidate methods against SMPRs for possible adoption as First Action *Official Methods*℠ for the prioritized ingredients

Advisory Panel

Chondroitin, anthocyanins, and phosphodiesterase type 5 (PDE5) inhibitors were the first ingredients ranked highest in order of need for standards and systematically reviewed analytical methods by the advisory panel of SPDS on December 19, 2013. The initial set of ingredients for standards development was selected from a list of some 75 ingredients developed in July 2011 under a previous NIH-AOAC contract (*see* sidebar). But, for ranking of the subsequent seven sets of ingredients, AOAC solicited industry to propose ingredients. Thus, the priority ingredients from sets 2–8 were chosen from a list that was the result of an ingredient ranking survey done in November 2014 with industry and trade input.

In reaching consensus on priority ingredients, the advisory panel (*see* sidebar for participating organizations) considered major driving factors, such as economic impact, research importance, regulatory concerns, safety concerns, risk of economic adulteration, and consumer use/relative market share of the ingredient. Other criteria included general availability of the methods from which to select a method, and availability of reference materials.

In addition to ranking and determining the scope for each priority ingredient, the advisory panel identified

working group chairs for the ingredients picked.

Stakeholder Panel/Working Groups

AOAC formed SPDS comprised of a diverse group of industry, technology providers, domestic and international regulators, and contract research organizations, among other key representatives. Ten stakeholder panel meetings were held to work toward consensus on setting standards. The first SPDS meeting was held on March 21, 2014, during the AOAC Mid-Year Meeting, where standards development activities began for chondroitin, anthocyanins, and PDE5 inhibitors. Stakeholders developed fitness-for-purpose statements, clearly stating the intended use of the methods.

Based on fitness-for-purpose statements, working groups, which are topic-specific subsets of the stakeholder panel, examined analytical issues and needs and developed draft SMPRs for each of the priority ingredients. AOAC convened 25 ingredient-specific working groups for this project.

AOAC SMPRs are voluntary consensus standards that describe the minimum performance criteria that methods must meet or exceed. SMPRs are developed by stakeholders in a highly controlled process that ensures that users, research organizations, government agencies, technology providers, and consumers work together to create a standard that meets the requirements of the user community.

AOAC held 10 SPDS meetings to reach consensus on standards.

Draft SMPRs for all priority ingredients were posted on the AOAC website for an open comment period, and all comments were carefully reviewed and reconciled, if necessary, by AOAC's chief scientific officer and working group chairs. SMPRs were reviewed and, if successful, approved by the stakeholder panel.

On March 16, 2018, at the AOAC Midyear Meeting, SPDS reviewed and approved SMPRs for the final set of priority ingredients: kavalactones, resveratrol, and skullcap (a third SMPR for skullcap limit test was approved in August 2018 during the AOAC Annual Meeting). With SMPRs approved for all 25 priority ingredients, AOAC successfully concluded this dietary supplements project with NIH-ODS.

ERPs

SMPRs are the valuable result of AOAC's standards development activities and are integrated into the AOAC *Official Methods*^{SM} systematic review process in which ERPs adopt methods that meet SMPRs. Once SMPRs are approved by the stakeholder panel, AOAC issues a call for methods and experts.

As part of the call for methods, AOAC offered method authors a one-on-one meeting with AOAC staff to review SMPRs and expectations of methods submission, and to answer any questions regarding submitting candidate methods. This opportunity with AOAC led to increased method author understanding of expectations for method submission applications and more complete packages for the ERPs to review.

Many of the AOAC ERPs for SPDS consisted of members who had participated on the respective ingredient-specific working group to ensure understanding of the rationale supporting development of the SMPRs. Review of methods by these ERP members was based on experience with the entire process and, in many cases, resulted in a more complete review.

ERPs, which are thoroughly vetted by the Official Methods Board (OMB), evaluated the best candidate methods against SMPRs for possible adoption as First Action *Official Methods*^{SM}. In addition to meeting SMPRs, candidate methods were carefully evaluated for completeness of method performance

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information, clarity, and ease of use, among other criteria.

On August 3–4, 2015, at AOAC headquarters in Rockville, Maryland, USA, an AOAC ERP on Dietary Supplements, chaired by **Brian Schaneberg** of Starbucks Coffee Co., evaluated candidate methods for chondroitin, anthocyanins, and PDE5 inhibitors and adopted methods for chondroitin and PDE5 inhibitors—the first ones under this contract. (For anthocyanins, the ERP agreed that none of the methods submitted met the SMPR, so no methods were approved for this ingredient.)

Six advisory panel meetings were held to identify and prioritize ingredients.

Most recently, AOAC ERPs granted Official First Action status to six methods during the AOAC Annual Meeting in August 2018: aloe vera, echinacea, ginseng, kavalactones (two), and ginger.

ERPs monitor First Action methods for 2 years of their adoption as they work their way toward Final Action status consideration. AOAC solicits user feedback on all First Action methods for consideration of a status change.

Approved SMPRs and First Action *Official Methods*℠ are codified and published in the *Journal of AOAC INTERNATIONAL* and *Official Methods of Analysis*.

Future Collaboration

Continuing the dietary supplements project is a priority for AOAC.

"The knowledge we've gathered from experts on this project is unprecedented," Sullivan said. "Their expertise is valuable, and AOAC is exploring strategies to continue the good work coming out of this project, which is something that everyone can be proud of."

AOAC continues to engage the advisory panel for a renewal effort to advance SPDS standards development activities, for example, revisiting SMPRs and convening ERPs for ingredients in which no methods have been approved. AOAC is also exploring other opportunities, such as training courses, consulting services, and a dietary supplement ingredient summit to identify and prioritize ingredient challenges and to encourage funding for additional ingredient working groups. It is hoped that the dietary supplements community will continue to make significant advancements through partnership with AOAC. ■

AOAC-NIH/ODS Dietary Supplements Projects Through the Years

This 5-year contract was one of a series of contracts that AOAC has held with NIH/ODS since September 2001, which started modestly enough with an agreement to find methods for the controversial supplement ephedra and aristolochic acid. The contract ended in March 2008, with an impressive list of methods developed and validated under challenging conditions. In the process, AOAC created and honed a technique for finding, evaluating, and validating methods that has been extended to other problems solved by the use of *Official Methods*℠.

"The overall body of work between AOAC and NIH/ODS is enormous," said **Darryl Sullivan** of Eurofins Food Integrity and Innovation and chair of the AOAC Stakeholder Panel on Dietary Supplements (SPDS). "The first contract took place from 2001 to 2008, and then annual contracts up to 2012."

As part of these prior contracts, AOAC delivered methods for aristolochic acid, ephedra (four), glucosamine, saw palmetto, coenzyme Q10, chondroitin, β-carotene, ginkgo, aflatoxins in ginger/ginseng, goldenseal, isoflavones, lycopene, and aconite. In addition, expert review panels (ERPs) were held from 2002 to 2010 for cranberry (organic acids and anthocyanins), echinacea, ginseng, lutein, milk thistle, MSM/DMSO, omega 3, SAMe, St. John's wort, turmeric, vitamin B_6, vitamin B_{12}, vitamin D, vitamin E, and yohimbe. Work was also in process for aloe, bitter orange, and green tea, however no ERPs were held for these ingredients.

AOAC produced a remarkable number of methods, and the Association learned a great deal about the process of reaching consensus and delivering the kinds of methods needed by industry. ■

AOAC Advisory Panel of SPDS

Council for Responsible Nutrition (CRN)
Herbalife
Natural Products Association (NPA)
NSF International
Synutra
U.S. Food and Drug Administration (FDA)
U.S. National Institutes of Health-Office of Dietary Supplements (NIH/ODS)
U.S. Pharmacopeia (USP) ■

SPDS Standards and Methods in Process: Status of Ingredients at a Glance (as of February 1, 2019)

Priority ingredient[a]	Working group chair	Start date	SMPR drafted	SMPR No./date approved	SMPR published	Call for experts/ methods	Candidate method(s) submitted	ERP	First Action method
FIRST SET									
Anthocyanins	Dana Krueger (Krueger Food Laboratories)	March 2014	July 2014	2014.007/ September 2014[b]	October 2014	October 2014	March 2015[c]	August 2015	
Chondroitin	Jana Hildreth (Synutra Pure)	March 2014	July 2014	2014.008/ September 2014	October 2014	October 2014	March 2015	August 2015	
				2014.009/ September 2014					**2015.11**
PDE5 inhibitors	Katerina Mastovska (Covance Laboratories)	March 2014	July 2014	2014.010/ September 2014	October 2014	October 2014	March 2015	August 2015	**2015.12**
				2014.011/ September 2014					
				2014.012/ September 2014					
SECOND SET									
Ashwagandha	Sanni Raju (Natreon, Inc.)	September 2014	December 2014	2015.007/ March 2015	April 2015	April 2015	September 2015[d]	December 2015	**2015.17**
Cinnamon	Milda Embuscado (McCormick and Co.)	September 2014	December 2014	2015.010/ March 2015	April 2015	April 2015	September 2015	December 2015/ July 2016	
Folin C	John Finley (Louisiana State University)	September 2014	December 2014	2015.009/ March 2015	April 2015	April 2015, December 2016	September 2015	December 2015/2017	**2017.13**
***Mitragyna speciosa* (kratom)**	Corey Hilmas (Natural Products Association)	September 2014	December 2014	2015.008/ March 2015	April 2015	April 2015, December 2016	September 2015	December 2015/2017	**2017.14**
THIRD SET									
Aloe in aloin	Prashant Ingle (Herbalife)	March 2015	June 2015	2015.015/ September 2015	October 2015	October 2015	April 2016	August 2016	**2016.09**
Tea	Yanjun Zhang (Herbalife)	March 2015	June 2015	2015.014/ September 2015	October 2015	October 2015	April 2016	August 2016	**2016.10**
Vitamin D	John Austad (Eurofins Food Integrity and Innovation)	March 2015	June 2015	2015.016/ September 2015 (Revised March 2017)	October 2015	October 2015			
FOURTH SET									
Collagen	Suhail Ishaq (BioCell Technology, LLC)	September 2015	December 2015	2016.005/ March 2016[e]	April 2016	August 2016	October 2016	December 2016	
Lutein (and esters)	Rick Myers (Kemin Industries, Inc.)	September 2015	December 2015	2016.004/ March 2016	April 2016	August 2016	October 2016	December 2016	
Turmeric (curcumins)	Aniko Solyom (GAAS Corp.)	September 2015	December 2015	2016.003/ March 2016	April 2016	August 2016	October 2016	December 2016	**2016.16**

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FIFTH SET									
Aloe vera	Kan He (Herbalife)	March 2016	June 2016	2017.009/ March 2017 2017.010/ March 2017	April 2017	August 2017	October 2017	December 2017	**2018.14**
Protein	Spencer Carter (Genysis Labs)	March 2016	June 2016	2016.013/ September 2016[f] 2016.014/ September 2016 2016.015/ September 2016 2016.016/ September 2016	November 2016	December 2016	November 2017	December 2017	**2017.12** **2017.11**
Vitamin B_{12}	Richard van Breemen (Oregon State University)	March 2016	June 2016	2016.017/ September 2016	November 2016	December 2016	November 2017	December 2017	
SIXTH SET									
Vitamins K_1 and K_2	Inger Reidun Aukrust (Kappa Biosciences)	September 2016	December 2016	2017.013/ March 2017[g]	April 2017	April 2017			
Free amino acids	Garrett Zielinski (Eurofins Food Integrity and Innovation)	September 2016	December 2016	2017.011/ March 2017	April 2017	April 2017	November 2017	December 2017	
Ginger	Anton Bzhelyansky (USP)	September 2016	December 2016	2017.012/ March 2017	April 2017	April 2017	November 2017	December 2017	**2018.04**
SEVENTH SET									
Echinacea	Stefan Gafner (American Botanical Council)	March 2017	June 2017	2017.015/ September 2017	October 2017	October 2017	April 2018	August 2018	**2018.08**
Ginseng	Paula Brown (British Columbia Institute of Technology)	March 2017	June 2017	2017.014/ September 2017	October 2017	October 2017	April 2018	August 2018	**2018.09**
SAMe	Joseph Zhou (Sunshineville Health Products)	March 2017	June 2017	2017.016/ September 2017	October 2017	October 2017	April 2018	August 2018	
EIGHTH SET									
Skullcap	Holly Johnson (American Herbal Products Association)	September 2017[h]	December 2017	2018.006/ March 2018[i] 2018.007/ March 2018	April 2018	April 2018	July 2018	August 2018	
Kavalactones	Steven Dentali (Dentali Botanical Sciences)	September 2017	December 2017	2018.005/ March 2018	April 2018	April 2018	July 2018	August 2018	2 *Official Methods*℠ to be codified
Resveratrol	Richard van Breemen (Oregon State University)	September 2017	December 2017	2018.004/ March 2018	April 2018	April 2018			

[a] The initiative is expected to result in *Standard Method Performance Requirements* (SMPRs®) for 25 priority dietary supplement ingredients/finished products. Ingredients are identified and prioritized at by the advisory panel for the AOAC Stakeholder Panel on Dietary Supplements as top ingredients for which systematically reviewed analytical methods are needed.
[b] AOAC Annual Meeting and Exposition, September 5, 2014, Boca Raton, Florida, USA.
[c] AOAC Mid-Year Meeting, March 21, 2015, Gaithersburg, Maryland, USA.
[d] AOAC Annual Meeting and Exposition, September 27–30, 2015, Los Angeles, California, USA.
[e] AOAC Mid-Year Meeting, March 14–18, 2016, Gaithersburg, Maryland, USA.
[f] AOAC Annual Meeting and Exposition, September 18–21, 2016, Dallas, Texas, USA.
[g] AOAC Mid-Year Meeting, March 13–17, 2017, Gaithersburg, Maryland, USA.
[h] AOAC Annual Meeting and Exposition, September 24–27, 2017, Atlanta, Georgia, USA.
[i] AOAC Mid-Year Meeting, March 12-16, 2018, Gaithersburg, Maryland, USA.
[j] AOAC Annual Meeting and Exposition, August 26–29, 2018, Toronto, Canada.