AOAC INTERNATIONAL

Stakeholder Panel on Dietary Supplements
Stakeholder Panel Meeting - March 17, 2016
Working Groups Meetings – March 18, 2016

Salon C/D
Gaithersburg Marriott Washingtonian Center
Gaithersburg, Maryland, 20878
USA

AOAC INTERNATIONAL

spds@aoac.org

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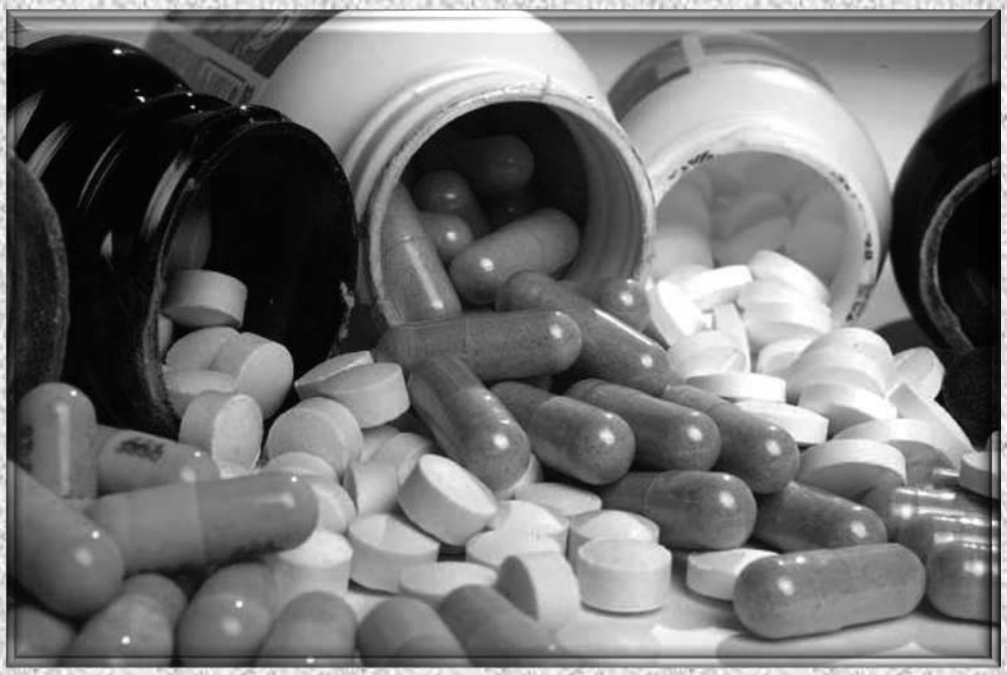

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STAKEHOLDER PANEL CHAIRS

DARRYL SULLIVAN, COVANCE LABORATORIES
Chair, AOAC Stakeholder Panel on Dietary Supplements

Darryl Sullivan is a Fellow of AOAC and has been an active member since 1980. He has served terms as secretary, president-elect, president, past president, and director of the Board of Directors, and previously served a three-year term as chair of the Official Methods Board, and is currently serving as Chair of the AOAC Stakeholder Panel on Infant Formula and Adult Nutritionals. In 2012 Darryl lead a very successful AOAC engagement with government and industry thought leaders in India and China on behalf of SPIFAN. He is also active with the Stakeholder Panel for Strategic Food Analytical Methods and the Stakeholder Panel for Agent Detection Assays. Sullivan also served a three-year term as a director on the AOAC Research Institute Board of Directors. He was a founding member and chair of the Presidential Task Force on Dietary Supplements and a member of the Task Force on Bacillus anthracis, as well as the AOAC Task Force on Nutrition Labeling and the AOAC Task Force on Sulfites. Prior to chairing the OMB, he served as a member and chair of the Methods Committee on Commodity Foods and Commodity Products. Sullivan was a founding member of the AOAC Technical Division on Reference Materials and served three terms on the Division's Executive Board. A staunch supporter of the Association, Sullivan was active in the e-CAM and Scholar I projects at AOAC, has exhibited at the annual meetings for many years, has presented hundreds of papers and posters at AOAC meetings and regularly publishes his research in the journal of the AOAC. He has also presented a significant number of papers on behalf of AOAC at other scientific meetings in many different parts of the world.

BRIAN SCHANEBERG, STARBUCKS COFFEE CO.
Vice Chair, AOAC Stakeholder Panel on Dietary Supplements

Brian Schaneberg, Ph.D., is the Global Scientific & Regulatory Affairs Director for Starbucks Coffee Company. Brian participates in the execution of company strategies while ensuring compliance and regulatory guidelines are met and followed by the company across all products: Starbucks, Teavana, Tazo, Evolution Fresh, La Boulange, and Ethos. Brian has over 15 years of natural products experience in the area of dietary supplements and herbals. Brian was also the Quality & Food Saftey and Scientific & Regulatory Affairs Director for Mars Botanical, a division of Mars, Inc. focusing on cocoa flavanol science and products. Before Mars Botanical, he was the Director of Technical Services at ChromaDex, Inc. in Irvine, California and was an Associate Research Scientist at the National Center for Natural Products Research at the University of Mississippi under the guidance of Dr. Ikhlas Khan, in a position funded by the US FDA for the development of methods to ensure the quality and safety of botanicals and dietary supplements. Over the years, Brian has worked closely with trade groups, industry, academia and government leaders. He has been a member of various review committees including NIH grants, analytical validation ERPs at AOAC and the Registry of Carcinogens. Brian also had the pleasure of holding an adjunct faculty position at the University of Colorado, Denver, advising a student that received his MS in Analytical Chemistry isolating phytochemicals and developing analytical testing procedures for Horse Chestnut. Brian has a Ph.D. in Organic Chemistry from Virginia Commonwealth University and a B.A. in Chemistry with a minor in Biology from Central College in Iowa. He has authored or co-authored more than 50 publications and presentations.

PRESENTER BIOS

Richard B. van Breemen, PhD
Matthias C. Lu Collegiate Professor of Pharmacy, Professor of Medicinal Chemistry and Pharmacognosy - University of Illinois College of Pharmacy

SPDS VITAMIN B_{12} WORKING GROUP

Richard B. van Breemen is the Matthias C Lu Collegiate Professor of Pharmacy and Professor of Medicinal Chemistry and Pharmacognosy at the University of Illinois College of Pharmacy. He serves as Director of the UIC/NIH Center for Botanical Dietary Supplements Research and leads the Mass Spectrometry, Metabolomics and Proteomics Facility for the University of Illinois Cancer Center. Prof. van Breemen received his B.A. in chemistry from Oberlin College in 1980 and Ph.D. in Pharmacology and Experimental Therapeutics from the Johns Hopkins University in 1985. He carried out post-doctoral research in laser desorption mass spectrometry at Johns Hopkins before joining North Carolina State University in 1994 and then the University of Illinois College of Pharmacy. He is a Regional Editor of *Biomedical Chromatography* and on the editorial board of *Assay and Drug Development Technologies.* Prof. van Breemen has received an Expert Methods Panel award from the AOAC International for his work on analytical methods for dietary supplements, the Harvey W. Wiley Award from the AOAC International, and the 2015 Researcher of the Year Award from the University of Illinois at Chicago. His research concerns the discovery and development of natural products as chemoprevention agents and the investigation of botanical dietary supplements as alternatives to hormone therapy for menopausal women.

SPENCER C ARTER

SPDS PROTEIN WORKING GROUP

Spencer Carter is Senior Vice President of Genysis Labs. Genysis Labs is a cGMP compliant, full service testing laboratory that has provided comprehensive analytical testing for the Dietary Supplement and Food & Beverage industries since 2008. Additionally, Genysis Labs specializes in developing patentable formulations in the field of sports nutrition. Backed by an ISO 17025:2005 accreditation and a management team of highly qualified scientists, Genysis Labs is committed to providing accurate and timely testing services while maintaining a laboratory environment consistent with ISO/IEC 17025:2005 requirements.

Spencer earned his Ph.D. in Analytical Chemistry from the University of Alberta, in Edmonton, Alberta, Canada. His thesis focused on the analysis of tamoxifen metabolites by non-aqueous capillary electrophoresis and mass spectrometry detection. Prior to Genysis Labs, he was Lab Director at Tandem Labs (now Covance). Tandem Labs

Spencer Carter (continued)

is a contract research organization (CRO) in the pharmaceutical industry performing bioanalytical services. His work included method development, validation, and sample analysis of biological samples. He focused on high-throughput analysis and improving efficiencies in the lab, as well as developing and maintaining non-proprietary assays. Previous to that, he was also the Bioanalytical Director at WIL Research and the Director of Bioanalytical Services at Pyxant Labs."

Jason W. Cooley, PhD

Research and Business development Scientist
BioCell Technology LLC

COLLAGEN WORKING GROUP PRESENTER

Jason W. Cooley received his PhD from Arizona State University (2001) where he conducted research aimed at the role of respiratory proteins in metabolic processes of biotechnologically important photosynthetic organisms. Dr. Cooley subsequently carried out his postdoctoral research investigating the role of respiration and bioenergetics in various disease paradigms and drug targets. Upon joining the faculty of the chemistry department at the University of Missouri in 2006, Dr. Cooley taught analytical and bioanalytical courses, while carrying out research understanding how membranes influence the biophysical events leading to aging related diseases such as Alzheimer's disease. Dr. Cooley recently returned home to Southern California in his current position with BioCell technology LLC where he acts as the Chief Science Officer for this premier collagen based dietary supplement manufacturer.

Kan He, Ph. D.
Principal Scientist
Botanical Development, Worldwide R&D, Herbalife

SPDS ALOE VERA WORKING GROUP

Kan He is responsible for development of botanical ingredients for Herbalife product line. He has been involved in botanical product design and development from lab scale to commercial production.

Before joined Herbalife, Kan He was in charge of research and development at Pure World Botanicals, Inc. and Naturex, Inc. respectively. He was responsible for developing new products and new processes, including scale up of plant extraction, purification, and chemical characterization of standardized herbal extracts.

Kan He graduated from the Shanghai University of Traditional Chinese Medicine with BSc and MSc in Pharmacy and Medicinal Chemistry. He received his Ph.D. in pharmacognosy from the Pharmaceutical Sciences, University of Arizona and completed his postdoctoral research at School of Pharmacy, Purdue University. Over the past twenty-

Kan He (Continued)

five years, he has been working in the area of natural products chemistry and authored or co-authored over 70 research papers on the peer reviewed scientific journals and book chapters. Kan He holds 11 US patents on the development of new herbal ingredients and new herbal manufacturing processes.

ANIKÓ SÓLYOM

SPDS TURMERIC WORKING GROUP

Anikó Sólyom, Ph.D. is the founder of GAAS Analytical, an independent contract testing laboratory with a focus on natural products and dietary supplements. She has 30+ years of comprehensive experience in analytical method development and method validation, using wide variety of analytical techniques to solve diverse problems.

Dr. Sólyom was selected in 2015 to serve a 5 year term as the member of the USP's Non-botanical Dietary Supplements Expert Committee. She is a member of the NIST/NIH DSQAP Advisory Board and serves on the AOAC's Expert Review Panel. She is the Chair of the AOAC SPDS Turmeric Working Group and a current member of several other AOAC working groups.

She has more than 40 papers published in peer-reviewed journals, and author of a patent. She holds B.S, M.S. and Ph.D. degrees in the areas of organic and analytical chemistry.

The Scientific Association Dedicated to Analytical Excellence®

Stakeholder Panel on Dietary Supplements (SPDS)

March 17, 2016 | 8:30AM – 5:00PM ET
Registration Opens at 7:30 a.m.

Gaithersburg Marriott Washingtonian Center | 9751 Washingtonian Blvd | Gaithersburg, MD, USA
Conference Room: Salon CD

A G E N D A

I. **Welcome and Introductions (8:30-8:40am)**
Jim Bradford (Executive Director, AOAC INTERNATIONAL), *Norma Hill* (President, AOAC INTERNATIONAL) and *Darryl Sullivan, Covance* (Chair, SPDS)

II. **Project Overview and Updates (8:40am – 8:50 am)**
   a. **Policies and Procedures**
   Darryl Sullivan

III. **Ingredient Updates (8:50am – 9:00am)**
   a. ERP Update (Ashwagandha, Folin C, Kratom)
   Darryl Sullivan
   b. Open Calls for Methods and Calls for Experts (Aloin, Cinnamon, Tea, Vitamin D)
   Darryl Sullivan

IV. **SMPR Presentations and Consensus**
   a. Set 4 Ingredient (Collagen, Lutein, and Turmeric) SMPR Presentations (9:00 am – 12:15 pm)
      i. Collagen* - *Suhail Ishaq, BioCell, Chair, Collagen Working Group* (9:00am – 10:00am)
      ii. Lutein* –*Rick Myers, Kemin; Chair, Lutein Working Group* (10:15am – 11:15am)
      iii. Turmeric* – *Aniko Solyom, GAAS Analytical; Chair, Turmeric Working Group* (11:15 am - 12:15pm)

V. **SPDS Advisory Panel Update (1:15 pm – 1:30 pm)**
Darryl Sullivan
   a. December 2015 Advisory Panel Meeting / Future Priorities

VI. **Launch of Set 5 Working Groups (1:30pm – 4:30pm)**
   a. Aloe Vera* (1:30 pm – 2:30 pm)
   Kan He, Herbalife (Chair, Aloe Vera Working Group)
   b. Protein* (2:45 pm – 3:45 pm)
   Spencer Carter Genysis Labs (Chair, Protein Working Group)
   c. Vitamin B12* (3:45 pm – 4:45 pm)
   Richard van Breemen, University of Illinois at Chicago - Vitamin B12 Working Group

VII. **Friday Working Group Schedule (4:40 pm – 4:50 pm)**
Darryl Sullivan

VIII. **Next Steps and Adjourn (4:50pm – 5:00 pm)**
Darryl Sullivan

Morning Break: 10:00am – 10:15am | Lunch (on your own): 12:15pm – 1:15pm | Afternoon Break 2:30pm – 2:45pm

**Item requires a vote by SPDS*

AOAC INTERNATIONAL Stakeholder Panel on Dietary Supplements
Working Group Sessions – March 18, 2016 (Day 2)
8:30 a.m. – 4:30 p.m., Salon CD

I. Protein (8:30 a.m. – 10:30 a.m.)
Chair: Spencer Carter, Genysis Labs
a. Review Fitness for Purpose
b. SMPR Development

II. Aloe Vera (11:00 a.m. – 2:00 p.m.)**
Chair: Kan He, Herbalife
a. Review Fitness for Purpose
b. SMPR Development

III. Vitamin B_{12} (2:30 p.m. – 4:30 p.m.)
Chair: Richard van Breemen, University of Illinois at Chicago
a. Review Fitness for Purpose
b. SMPR Development

****Day 2 Lunch: On your own, 12:00 p.m. – 1:00 p.m.**

**Item requires a vote by SPDS*

Update on the Stakeholder Panel on Dietary Supplements(SPDS)

Darryl Sullivan, Chair
Stakeholder Panel on Dietary Supplements
Covance Laboratories

March 2016

AOAC SPDS History

- AOAC INTERNATIONAL signed a 5-year contract with the National Institutes of Health-Office of Dietary Supplements (NIH/ODS) to establish voluntary consensus standards for high-priority ingredients.
- Develop 25 standard method performance requirements (SMPRs) for priority dietary supplement ingredients.
- Deliver First Action *Official Methods*SM for the prioritized dietary supplement ingredients
- Encourage participation with the dietary supplements industry to develop voluntary consensus standards.

AOAC SPDS 5 Year Plan

- **5 Advisory Panel Meetings** to identify key stakeholders, subject matter experts, frames the issues, determine ingredients, and set priorities for the stakeholder panel.
- **10 Stakeholder Panel Meetings** to deliberate and approve voluntary consensus standards.
- **25 Total Working Groups** to draft and recommend SMPRs.
- **8 Expert Review Panel Meetings** to review and potentially adopt fit for purpose First Action *Official Methods*SM for 25 ingredients.

Stakeholder Panel on Dietary Supplements (SPDS)

- Update on Ingredients:
  - Set 2 ERP held on December 2015
    - Ashwagandha, Folin C, and Mitragyna speciosa – 1 AOAC First Action *Official Method*SM Status for Ashwagandha
    - Cinnamon ERP slated for June 2016
  - Set 3 Call for Methods and Experts posted on AOAC Web site
    - Aloe, Tea, and Vitamin D
    - ERP slated for June 2016
  - Set 4 SMPRs to be recommended at AOAC SPDS March 2016
    - Collagen, Lutein (and Esters) , and Turmeric

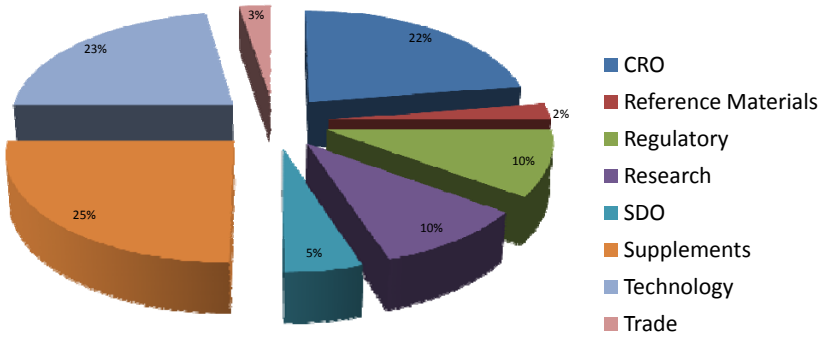
Stakeholder Panel on Dietary Supplements (SPDS)

- Update on Ingredients:
  - Launch for set 5 slated for 2016 AOAC Midyear SPDS Meeting
    - Aloe vera, Chair - Kan He (Herbalife)
    - Protein, Chair - Spencer Carter (Genysis Labs)
    - Vitamin B_{12}, Chair - Richard van Breeman (University of Illinois at Chicago)
  - Launch for set 6 slated for 2016 AOAC Annual Meeting SPDS Meeting
    - Vitamin K_1 and K_2, Chair TBD
    - Free amino acids, Chair TBD
    - Ginger, Chair TBD

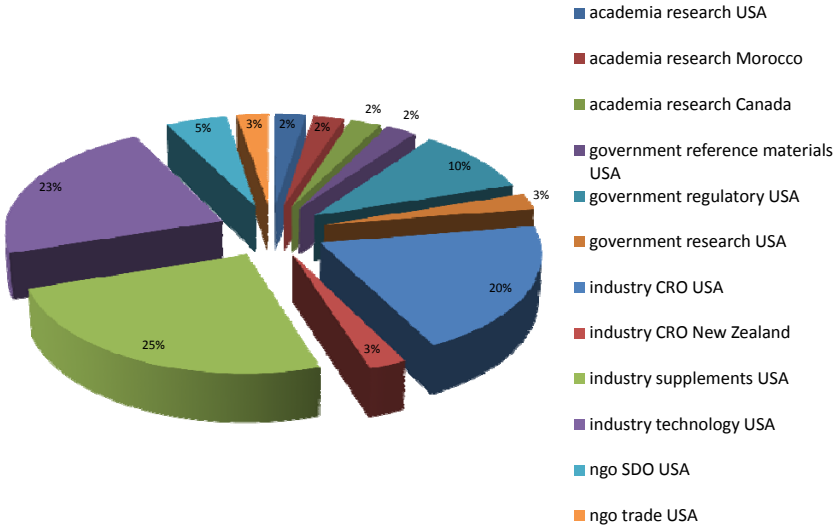
Stakeholder Panel on Dietary Supplements (SPDS)

- SPDS Advisory Panel slated for fall 2016 to prioritize next 6 ingredients for 2017
- Advisory Panel includes representatives from AHPA, CRN, CHPA, NSF, NPA, NIH, USP, Herbalife, and Synutra Pure

SPDS BY SPECIFIC PERSPECTIVES



SPDS - ALL PERSPECTIVES



AOAC SPDS Publications

- Nutraceuticals World
  - Six More Dietary Ingredients Picked for Analytical Evaluation, by Richard A. Lovett, JD, PhD
- JAOAC
  - Jan/Feb Articles on Chondroitin and PDE5 Inhibitors
  - Encourage submit work to JAOAC

Call for Methods and Call for Experts

- Call for Method and the Call for Experts is posted on the AOAC web site for the set 3 ingredients:
  - Aloin in Aloe
  - Tea
  - Vitamin D
- Deadline for Methods and CVs is April 29

How do you get involved?

- Submit methods on the Call for Methods tab at www.aoac.org
- Volunteer for Expert Review Panels on the Call for Experts tab at www.aoac.org
- SPDS site at www.aoac.org, click "Standards", then Stakeholder Panel on Dietary Supplements (SPDS) for complete information about the program

Contact Information

Darryl Sullivan, Chair SPDS

Covance Laboratories

Tel: 608.242.2711

Email: darryl.sullivan@covance.com

Contact AOAC Staff:

Tel: 301.924.7077

Web: www.aoac.org

- **Jim Bradford**, Executive Director/CEO, jbradford@aoac.org, ext. 102
- **Deborah McKenzie**, Sr. Director, Standards Development and AOAC Research Institute, dmckenzie@aoac.org, ext. 157
- **Dawn Frazier**, Sr. Executive for Scientific Business Development, dfrazier@aoac.org, ext. 117

AOAC INTERNATIONAL STAKEHOLDER PANEL ON DIETARY SUPPLEMENTS

Suhail Ishaq and Jason Cooley, BioCell
Collagen Working Group
March 17, 2016

Gaithersburg, Maryland

Fitness for Purpose

The method should be able to:

Quantify total native (undenatured) and hydrolyzed collagen type I, II & III in the raw materials and final finished dosage forms including but not limited to dry powders, tablets, capsules, softgels and liquids .
Individually separate and quantify native (undenatured) and hydrolyzed collagen type I, II & III if blended together.

Collagen Working Group Members

Suhail Ishaq, BioCell Technology (Chair)
Ali Asim, BioCell Technology
Maria Bojstrup, Pfizer
Jason Cooley, BioCell Technology
Linda Dodd, PB Gelatins/PB Leiner
Christine Farthing, Pfizer
Prashang Ingle, Herbalife
Adam Kuszak, NIH
Elizabeth Mudge, BCIT
Curtis Phinney, Curtis Phinney CNS
Lars Reimann, Eurofins
Brian Schaneberg, Starbucks
Darryl Sullivan, Covance
John Szpylka, Merieux Nutrisciences
John Travis, NSF International
Denise Walters, Pfizer
Kurt Young, GNC/Nutra Manufacturing
Joseph Zhou, Sunshineville Health Products
Garrett Zielinski, Covance

Collagen Working Group Work to Date

- 1 In Person Meeting
- 3 teleconferences (November 2015 – December 2015)
- 1 SMPR Drafted
- Public comment period (January 8, 2016 – February 5, 2016)
- SMPRs made ready for SPDS review and approval

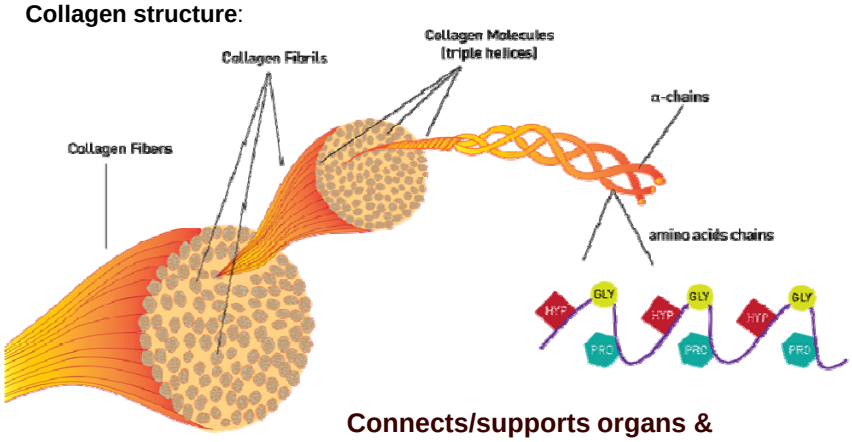
Background

Collagen:

- Main structural protein in the extracellular space in various connective tissues in animals.
- Primary component of connective tissue
- Most abundant protein in mammals (~25% to 35% of protein content).
- Over 30 “Types”:
    1. Fibrillar (Types I, II, III, V, XI)
    2. non-fibrillar (all the rest) .

Background

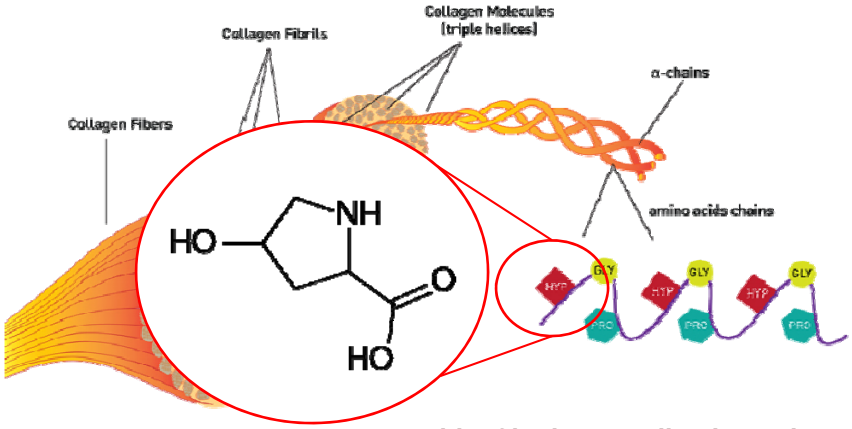
Collagen structure:



Connects/supports organs & tissues
(e. g. **skin**, bone, blood vessels, tendons, muscles, and **cartilage**)

Background

Collagen structure (hydoxyproline):



Wealth of hydroxyproline is marker of collagen fibrils

Main Collagen Types

Type	Location/Function
I	Skin, Tendons , Bones, Arteries, Cornea, Scar tissue
II	Joints, Hyaline cartilage, vitreous humour
III	Skin, granulation tissue, reticular fiber
IV	Basal lamina, eye lens, capillaries, kidney

More than 14 types defined, but types I-IV are most abundant

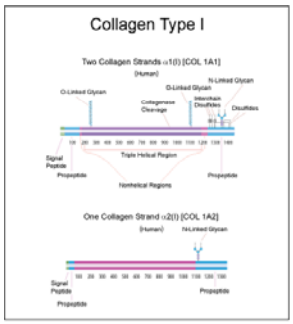
Background

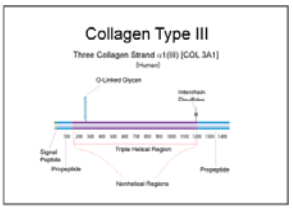
Amino acid sequences differ between collagen proteins by > 40% sequence identity

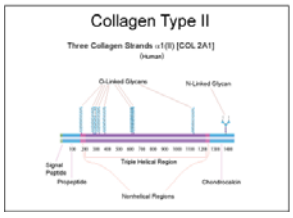
posttranslational modifications are different as well.

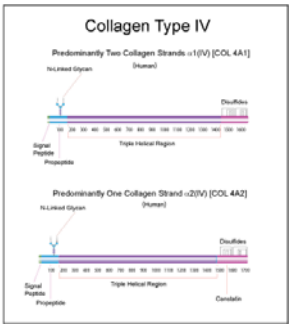
e.g. type II α1 protein can have ten-fold more hydroxylation at Proline and glycosylation events at its lysine residues than similar Type I protein.

Background









Commercial Collagen Products

1. **Gelatin**:
   - an irreversibly denatured (Heat or Acid) form of collagen (usually types I & III) used in food and cosmetics industry

2. **Partially denatured** (physical breakdown) **or non-hydrolyzed :**
   - All types (I/III and II are most common)
   - High molecular weight
   - Limited water solubility (soluble in mildly acidic solutions)

3. **Hydrolyzed**
   - Type I/III (derived from beef, pig or fish skin and bones)
   - Type II (usually from chicken sternal cartilage), can be

SMPR Key Points

Applicability:
The method will be able to identify and quantify individual native (un-denatured) and hydrolyzed collagen type I, II & III if one or multiple types are present in dietary ingredients and dietary supplement finished products.

Validation Guidance:
Data demonstrating that a candidate method is able to: Separate a combination of native collagen type I, II and III and/or hydrolyzed collagen type I, II and III. Quantify each individual collagen type both native and hydrolyzed.

Table 1: Method performance requirements

Parameter	Criteria
Analytical Range (%)	1 – 100
LOQ (%)	0.5
Recovery (%)	90-110
% RSD_r	≤ 5
% RSD_R	≤ 10

Comments Submitted (if any)

- No comments submitted

Motion

- Move to accept the Standard Method Performance Requirements for Collagen as presented.

Discussion?

DRAFT AOAC SMPR 2015.XXX; Version 3; December 17, 2015

Quantitation of Collagen

Intended Use: Reference method for cGMP compliance.

1. **Purpose:** AOAC SMPRs describe the minimum recommended performance characteristics to be used during the evaluation of a method. The evaluation may be an on-site verification, a single-laboratory validation, or a multi-site collaborative study. SMPRs are written and adopted by AOAC Stakeholder Panels composed of representatives from the industry, regulatory organizations, contract laboratories, test kit manufacturers, and academic institutions. AOAC SMPRs are used by AOAC Expert Review Panels in their evaluation of validation study data for method being considered for *Performance Tested Methods* or AOAC *Official Methods of Analysis*, and can be used as acceptance criteria for verification at user laboratories.

2. **Applicability**:
The method will be able to identify and quantify individual native (un-denatured) and hydrolyzed collagen type I, II & III if one or multiple types are present in dietary ingredients and dietary supplement finished products.

3. **Analytical Technique**:
Any analytical technique(s) that measures the analytes of interest and meets the following method performance requirements is/are acceptable.

4. **Definitions**:

Collagen

A triple helix protein that generally consists of two identical chains (α1) and an additional chain that differs slightly in its chemical composition (α2). The amino acid composition of collagen is notable for its particularly high hydroxyproline content. The three most common types of collagen are: type I, found in skin, tendon, vascular ligature, organs, bone (main component of the organic part of bone); type II, found in cartilage (main collagenous component of cartilage); and type III, found in reticular fibers.

Structures:

http://www.sigmaaldrich.com/life-science/metabolomics/enzyme-explorer/learning-center/structural-proteins/collagen.html

Dietary Ingredients
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 total dietary intake; or a concentrate, metabolite, constituent, extract, or combination of any of the above dietary ingredients.[1]

Dietary supplements

[1] Federal Food Drug and Cosmetic Act §201(ff) [U.S.C. 321 (ff)

A product intended for ingestion that contains a "dietary ingredient" intended to add further nutritional value to (supplement) the diet. Dietary supplements may be found in many forms such as tablets, capsules, softgels, gelcaps, liquids, or powders.

Hydrolyzed Collagen
Peptides and polypeptides rich in hydroxyproline, produced by breaking down the molecular bonds of native collagen strands using one or more combinations of physical, chemical, or biological methods.

Limit of Quantitation (LOQ)
The minimum concentration or mass of analyte in a given matrix that can be reported as a quantitative result.

Quantitative method
Method of analysis whose response is the amount of the analyte measured either directly (enumeration in a mass or a volume), or indirectly (color, absorbance, impedance, etc.) in a certain amount of sample.

Repeatability
Variation arising when all efforts are made to keep conditions constant by using the same instrument and operator and repeating during a short time period. Expressed as the repeatability standard deviation (SD_r); or % repeatability relative standard deviation (%RSD_r).

Reproducibility
The standard deviation or relative standard deviation calculated from among-laboratory data. Expressed as the reproducibility standard deviation (SD_R); or % reproducibility relative standard deviation (% RSD_R).

Recovery
The fraction or percentage of spiked analyte that is recovered when the test sample is analyzed using the entire method.

5. **Method Performance Requirements**:
See table 1.

6. **System suitability tests and/or analytical quality control:**
Suitable methods will include blank check samples, and check standards at the lowest point and midrange point of the analytical range.

7. **Reference Material(s):**
Refer to Annex F: *Development and Use of In-House Reference Materials* in Appendix F: *Guidelines for Standard Method Performance Requirements*, 19th Edition of the AOAC INTERNATIONAL Official Methods of Analysis (2012). Available at: http://www.eoma.aoac.org/app_f.pdf

Identify suitable materials for method validation

8. **Validation Guidance**:
Requirement for consideration as an AOAC *Official Methods of Analysis*:

Data demonstrating that a candidate method is able to: Separate a combination of native collagen type I, II and III and/or hydrolyzed collagen type I, II and III. Quantify each individual collagen type both native and hydrolized.

Appendix D: Guidelines for Collaborative Study Procedures To Validate Characteristics of a Method of Analysis; 19th Edition of the AOAC INTERNATIONAL Official Methods of Analysis (2012). Available at: http://www.eoma.aoac.org/app_d.pdf

Appendix F: Guidelines for Standard Method Performance Requirements; 19th Edition of the AOAC INTERNATIONAL Official Methods of Analysis (2012). Available at: http://www.eoma.aoac.org/app_f.pdf

Appendix K: Guidelines for Dietary Supplements and Botanicals; 19th Edition of the AOAC INTERNATIONAL Official Methods of Analysis (2012). Available on line at: http://www.eoma.aoac.org/app_k.pdf

9. **Maximum Time-To-Result:** None

116
117 **Table 1: Method performance requirements**

Parameter	Criteria
Analytical Range (%)	1 – 100
LOQ (%)	0.5
Recovery (%)	90-110
% RSD_r	≤ 5
% RSD_R	≤ 10

Table 2: Matrices

tablets
capsules
softgels
powders
liquids
chewables

Stakeholder panel on dietary supplements

Background and Fitness for Purpose

Lutein and Related Xanthophylls

Rick Myers, Kemin
Lutein Working Group
March 17, 2016

Gaithersburg, Maryland

Fitness for Purpose

Quantitative measurement of the following in both raw materials and dietary supplements:

- Lutein
- 3'-Epilutein
- Zeaxanthin
- β-Cryptoxanthin

Lutein Working Group Members

Rick Myers, Kemin (Chair)
Maria Bøjstrup, Pfizer
Neil Craft, Craft Technologies
April Hall, Nutra Manufacturing
Fred Khachik, Kemin Industries
David Kennedy, Phenomenex
Elizabeth Mudge, BCIT
Melissa Phillips, NIST
Tom Phillips, MD Department of Agriculture
Lanette Richards, TBAR
Catherine Rimmer, NIST
Brian Scheneberg, Starbucks
Aniko Solyom, GAAS Analytical
Darryl Sullivan, Covance
John Spzylka, Mérieux NutriScience
Denise Walters, Pfizer
Jinchaun Yang, Waters
Tyler White, TBAR
Garrett Zielinski, Covance

Lutein Working Group Work to Date

- 1 in-person meeting
- 3 teleconferences (November 2015 – December 2015)
- 1 SMPR Drafted
- Public comment period (January 8, 2016 – February 5, 2016)
- SMPRs made ready for SPDS review and approval

Background

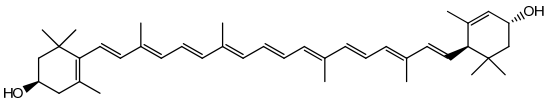
Carotenoids are a diverse family of botanical pigments
Minimal biosynthesis in animals; so must derive from diet
Botanical function
- Mediate photoinduced electron transfer to chlorophyll
- Quench singlet/triplet-chlorophyll that can damage allied tissues during very active photosynthesis

Two relevant carotenoid families
- *Carotenes:* hydrocarbons (orange)
- *Xanthophylls*: hydroxylated carotenes (yellow)

Only xanthophylls of interest here. Dozens exist!
- **Often exists as fatty acid esters in nascent tissue**

1. Lutein

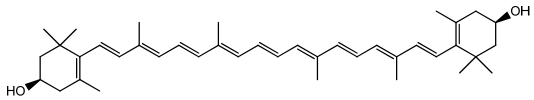
- (3R,3'R,6'R)-β,ε-Carotene-3,3'-diol*;* **dietary**
- Commercial and supplemental roles
  - Accumulates throughout human retina
  - Reportedly rescues AMD
  - Present in other tissues, relevance under study
  - Colors white egg yolks yellow
  - Antioxidant
  - Colorant (E161b)
- Structure



- Proposed daily dose: 10 mg

2. Zeaxanthin

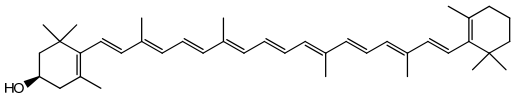
- β,β-Carotene-3,3'-diol; **dietary**
- Zeaxanthin differs from lutein only by placement of single double bond.
- Commercial and supplemental roles
  - Also accumulates in human retina; predominates in *macula lutea*
  - Reportedly rescues AMD
  - Colors white egg yolks yellow
  - Colorant (E161h)
- Structure



- Proposed daily dose: 2 mg

3. β-Cryptoxanthin

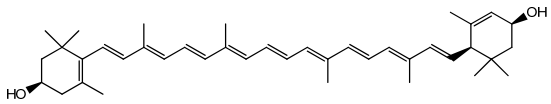
- (3R,3'R,6'R)-β,ε-Carotene-3,3'-diol; **dietary**
- Commercial and supplemental roles
  - Provitamin in humans; converted to vitamin A
  - Possible antioxidative DNA protection, bone health, others
  - Colorant (E161c) in Australia and New Zealand; not in US or EU
- Structure



- Proposed daily dose: 4 mg

4. 3’-Epilutein

- (3R,3’S,6’R)-Lutein
- **Not dietary—**no biological or commercial role
- Significant epimer product and loss of lutein
  - Occurs in aqueous acid
  - Reaction likely proceeds by S_N1 and S_N2, but mostly S_N2 since conversion exceeds 50%
- Structure



General Analytical Needs

Method should

- Quantitatively de-esterify all analyte forms
- Separate and accurately quantify relevant free analytes
  - Lutein
  - Zeaxanthin
  - β-Cryptoxanthin
  - 3’-Epilutein (principal lutein metabolite)
- Determine the above in
  - Raw materials used in dietary supplement formulations
  - Finished products

SMPR criteria

Applicability

Separate quantitative determination of β-cryptoxanthin, lutein, and zeaxanthin in ingredients and dietary supplements.

Analytical Technique(s)

Any analytical technique that resolves and quantifies the analytes of interest and meets the following method performance requirements is acceptable.

Method Performance Requirements

Analytical Range and LOQ Requirements

Analytical Range	0.0005% to 100%
	5 to 1,000,000 ppm
Limit of Quantitation (LOQ)	2ppm
	0.0002%

Recovery, Repeatability, and Reproducibility Parameters

Range	5 to 20 ppm	>20 to 1000 ppm	>0.1% to 1%	>1%
Recovery	80 to 110%	95 to 105%	97 to 102%	98 – 102%
Repeatability	8	5	4	2
Reproducibility	12	8	6	3

Matrices

- Tablets
- Capsules
- Liquids
- Powders
- Extracts
- Plant products

Comments Submitted

1. Delete “NIST list of lutein, zeaxanthin, and β-cryptoxanthin in foods” since levels are much too low and not applicable. **DONE**
2. Change reference material entry to read “NIST SRM 3280 Multivitamin/Multi-element Tablets.” **DONE**
3. Typos: spelling (matrix, tables) and remove comma. **DONE**

Motion

- Motion to accept the Standard Method Performance Requirements for Lutein as presented.

Discussion?

DRAFT AOAC SMPR 2016.XXX; Version 4; November 19, 2015

SMPR Name: Quantitative measurement of β-cryptoxanthin, lutein, and zeaxanthin in ingredients and dietary supplements.

Intended Use: Reference method for cGMP compliance.

1. Purpose

AOAC SMPRs describe the minimum recommended performance characteristics to be used during the evaluation of a method. The evaluation may be an on-site verification, a single-laboratory validation, or a multi-site collaborative study. SMPRs are written and adopted by AOAC Stakeholder Panels composed of representatives from the industry, regulatory organizations, contract laboratories, test kit manufacturers, and academic institutions. AOAC SMPRs are used by AOAC Expert Review Panels in their evaluation of validation study data for method being considered for *Performance Tested Methods* or AOAC *Official Methods of Analysis*, and can be used as acceptance criteria for verification at user laboratories. [Refer to Appendix F: *Guidelines for Standard Method Performance Requirements*, *Official Methods of Analysis of AOAC INTERNATIONAL* (2012) 19th Ed., AOAC INTERNATIONAL, Gaithersburg, MD, USA.]

2. Applicability:

Separate quantitative determination of β-cryptoxanthin, lutein, and zeaxanthin in ingredients and dietary supplements.

3. Analytical Technique:

Any analytical technique(s) that measures the analytes of interest and meets the following method performance requirements is/are acceptable.

4. Definitions:

Analytes

β-Cryptoxanthin

IUPAC name: (R)-3,5,5-Trimethyl-4-[3,7,12,16-tetramethyl-18-(2,6,6-trimethylcyclohex-1-enyl)-octadeca-1,3,5,7,9,11,13,15,17-nonaenyl]-cyclohex-3-enol. CAS registry number: 472-70-8. See figure 1 for chemical structure.

Lutein

IUPAC name: β,ε-carotene-3,3'-diol. CAS registry number 1 27-40-2. See figure 2 for chemical structure.

Zeaxanthin

IUPAC name: 4-[18-(4-hydroxy-2,6,6-trimethyl-1-cyclohexenyl)-3,7,12,16-tetramethyl-octadeca-1,3,5,7,9,11,13,15,17-nonaenyl]-3,5,5-trimethyl-cyclohex-3-en-1-ol. CAS registry number: 144-68-3. See figure 3 for chemical structure.

Dietary Ingredients
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 total dietary intake; or a concentrate, metabolite, constituent, extract, or combination of any of the above dietary ingredients.[1]

Dietary Supplements
A product intended for ingestion that contains a "dietary ingredient" intended to add further nutritional value to (supplement) the diet. Dietary supplements may be found in many forms such as tablets, capsules, softgels, gelcaps, liquids, or powders.

Limit of Quantitation (LOQ)
The minimum concentration or mass of analyte in a given matrix that can be reported as a quantitative result.

Quantitative method
Method of analysis which response is the amount of the analyte measured either directly (enumeration in a mass or a volume), or indirectly (color, absorbance, impedance, etc.) in a certain amount of sample.

Repeatability
Variation arising when all efforts are made to keep conditions constant by using the same instrument and operator and repeating during a short time period. Expressed as the repeatability standard deviation (SD_r); or % repeatability relative standard deviation ($\%RSD_r$).

Reproducibility
The standard deviation or relative standard deviation calculated from among-laboratory data. Expressed as the reproducibility relative standard deviation (SD_R); or % reproducibility relative standard deviation ($\% RSD_R$).

Recovery
The fraction or percentage of spiked analyte that is recovered when the test sample is analyzed using the entire method.

5. Method Performance Requirements:
See table 1 and 2.

6. System suitability tests and/or analytical quality control:
Suitable methods will include blank check samples, and check standards at the lowest point and midrange point of the analytical range.

7. Reference Material(s):
Refer to Annex F: *Development and Use of In-House Reference Materials* in Appendix F: *Guidelines for Standard Method Performance Requirements*, 19th Edition of the AOAC INTERNATIONAL Official Methods of Analysis (2012). Available at: http://www.eoma.aoac.org/app_f.pdf

USP Lutein
USP Zeaxanthin

[1] Federal Food Drug and Cosmetic Act §201(ff) [U.S.C. 321 (ff)

NIST 3280 Lutein (Multivitamin)
NIST list of lutein, zeaxanthin, and β-cryptoxanthin in foods

8. Validation Guidance:

Appendix D: Guidelines for Collaborative Study Procedures To Validate Characteristics of a Method of Analysis; 19th Edition of the AOAC INTERNATIONAL Official Methods of Analysis (2012). Available at: http://www.eoma.aoac.org/app_d.pdf

Appendix F: Guidelines for Standard Method Performance Requirements; 19th Edition of the AOAC INTERNATIONAL Official Methods of Analysis (2012). Available at: http://www.eoma.aoac.org/app_f.pdf

Appendix K: Guidelines for Dietary Supplements and Botanicals; 19th Edition of the AOAC INTERNATIONAL Official Methods of Analysis (2012). Available on line at: http://www.eoma.aoac.org/app_k.pdf

All matrices in table 3 shall be evaluated, or the scope (applicability) of AOAC-adopted method must expressly state the applicable dietary supplement forms.

9. Maximum Time-To-Result: None

Table 1: Analytical Range and LOQ Requirements

Analytical Range	0.0005% to 100%
	5 to 1,000,000 ppm
Limit of Quantitation (LOQ)	≤ 0.0002%
	≤ 2 ppm

Table 2: Recovery, Repeatability, and Reproducibility Parameters

Range	**5 to 20 ppm**	**>20 to 1000ppm**	**>0.1% to 1%**	**>1%**
% Recovery	80 to 110	95 to 105	97 to 102	98 – 102
% RSDr	≤ 8	≤ 5	≤ 4	≤ 2
% RSD_R	≤ 12	≤ 8	≤ 6	≤ 3

% recovery, % RSDr, and % RSD_R shall be determined individually for each claimed matrice.

Table 3: Matrices

Tablets
Capsules
Liquids
Powders
Extracts
Plant products
Gummies

Figure 1: Chemical structure of all-*trans* β-cryptoxanthin.

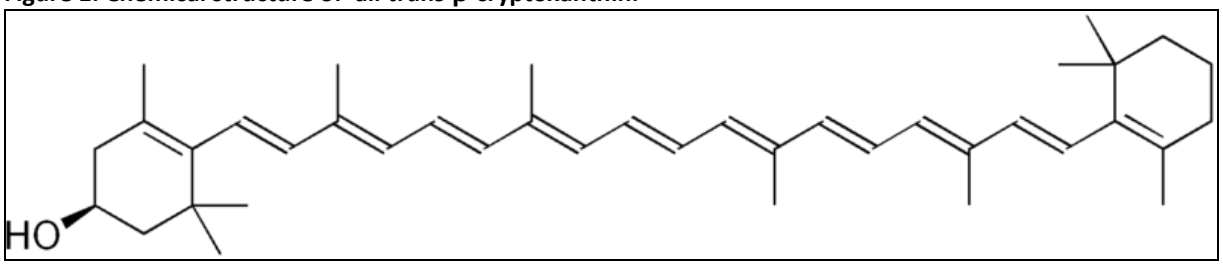


Figure 2: Chemical structure of all-*trans* lutein.

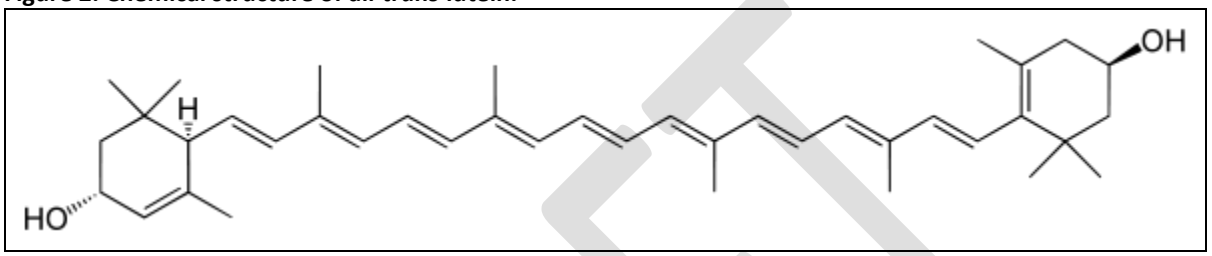
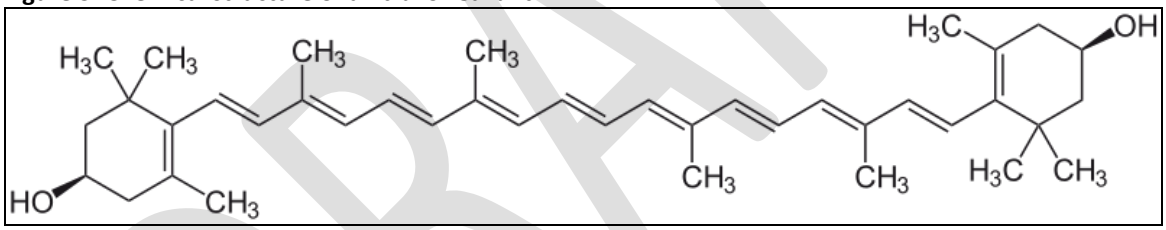


Figure 3: Chemical structure of all-*trans* zeaxanthin.



DRAFT

AOAC INTERNATIONAL STAKEHOLDER PANEL ON DIETARY SUPPLEMENTS

Anikó Sólyom, GAAS Analytical

Turmeric Working Group

March 17, 2016

Gaithersburg, Maryland

Fitness for Purpose

The method will be able to quantify total curcuminoid content, calculated as the sum of curcumin, demethoxycurcumin, and bis-demethoxycurcumin, in turmeric [*Curcuma longa* Linn.] rhizome, powdered botanical raw materials, extracts, and dietary supplement finished products containing turmeric extract, alone or in combination with other dietary ingredients. The method must be able to separate and quantify each individual curcuminoid.

Turmeric Working Group Members

Anikó Sólyom, GAAS Analytical (Chair)
Joseph Betz, NIH ODS
Paula Brown, BCIT
Nicole Chrisafis, Gaia Herbs
David Kennedy, Phenomenex
Adam Kuszak, NIH ODS
Elizabeth Mudge, BCIT
Melissa Phillips, NIST
Tom Phillips, MD Department of Agriculture
Lanette Richards, TBAR
Kate Rimmer, NIST
Brian Schaneberg, Starbucks
Bernice Sauza, TBAR
Jules Skamarack, Eurofins
Darryl Sullivan, Covance
John Szpylka, Mérieux NutriSciences
John Travis, NSF International
Jinchaun Yang, Waters
Joseph Zhou, Sunshineville

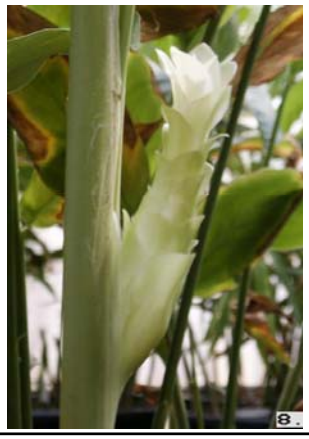
Turmeric Working Group Work to Date

- 1 In Person Meeting
- 3 teleconferences (November 2015 – December 2015)
- 1 SMPR Drafted
- Public comment period (January 8, 2016 – February 5, 2016)
- SMPRs made ready for SPDS review and approval

Background

Turmeric (*Curcuma longa* L.)

Common names: turmeric, turmeric root, Indian saffron
Member of the ginger family, Zingiberaceae



Turmeric rhizoma

Background

Uses

Culinary:

- flavoring and coloring agent
- main spice in curry

Traditional Chinese and Ayurvedic medicine:

- topical application for eczema and wound healing
- aid digestion and liver function
- relieve arthritis pain
- regulate menstruation

Current research:

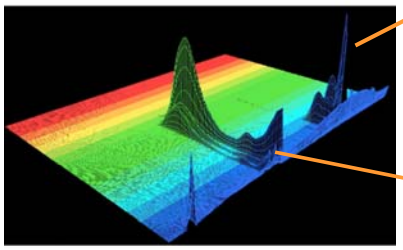
- osteoarthritis, Alzheimer disease, eye inflammation,
- colorectal cancer, Crohn's disease, diabetes, stomach upset
- gingivitis, stomach ulcer, irritable bowel syndrome, RA and more.

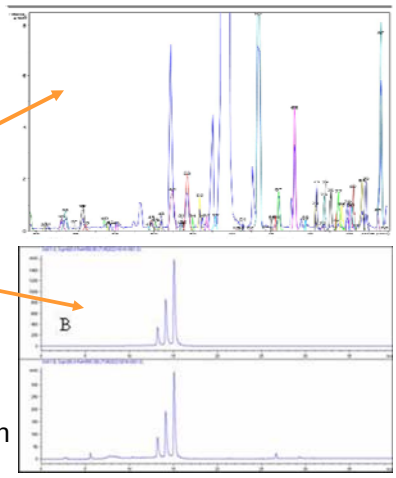
Source: NCCIH Dietary Supplement Database (https://nccih.nih.gov/health/turmeric/ataglance.html

Background

Turmeric (*Curcuma longa* L.)

Spectra of turmeric extract

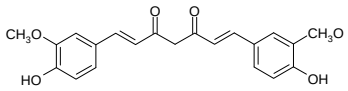




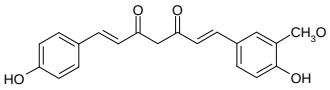
Approx. 5% of the plant is curcumin

Background

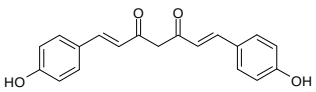
Curcuminoids



Curcumin
MW:368



Demethoxycurcumin
MW:338



Bisdemethoxycurcumin
MW:308

Background

Significance

- In the Dietary Supplement Database (DSLD) 1,044 products contained turmeric and/or curcumin(oids) and/or extracts (out of total 42,000 DS)
- 47% of these products turmeric/curcumin as a component of a blend

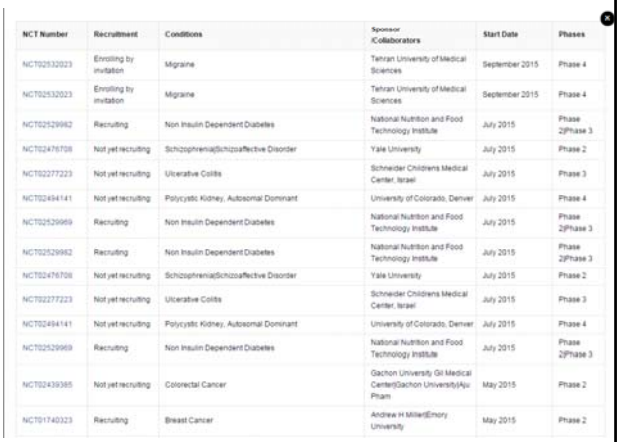
Source: Leila G. Saldanha, PhD, RD, Office of Dietary Supplement, NIH. Personal communication

Background

Significance

190 clinical trials between 1996 and 2015

(http://clinicaltrials.gov)



NCT Number	Recruitment	Conditions	Sponsor /Collaborators	Start Date	Phases
NCT02532023	Enrolling by invitation	Migraine	Tehran University of Medical Sciences	September 2015	Phase 4
NCT02532023	Enrolling by invitation	Migraine	Tehran University of Medical Sciences	September 2015	Phase 4
NCT02529982	Recruiting	Non Insulin Dependent Diabetes	National Nutrition and Food Technology Institute	July 2015	Phase 2|Phase 3
NCT02476708	Not yet recruiting	Schizophrenia|Schizoaffective Disorder	Yale University	July 2015	Phase 2
NCT02277223	Not yet recruiting	Ulcerative Colitis	Schneider Childrens Medical Center, Israel	July 2015	Phase 3
NCT02494141	Not yet recruiting	Polycystic Kidney, Autosomal Dominant	University of Colorado, Denver	July 2015	Phase 4
NCT02529969	Recruiting	Non Insulin Dependent Diabetes	National Nutrition and Food Technology Institute	July 2015	Phase 2|Phase 3
NCT02529982	Recruiting	Non Insulin Dependent Diabetes	National Nutrition and Food Technology Institute	July 2015	Phase 2|Phase 3
NCT02476708	Not yet recruiting	Schizophrenia|Schizoaffective Disorder	Yale University	July 2015	Phase 2
NCT02277223	Not yet recruiting	Ulcerative Colitis	Schneider Childrens Medical Center, Israel	July 2015	Phase 3
NCT02494141	Not yet recruiting	Polycystic Kidney, Autosomal Dominant	University of Colorado, Denver	July 2015	Phase 4
NCT02529969	Recruiting	Non Insulin Dependent Diabetes	National Nutrition and Food Technology Institute	July 2015	Phase 2|Phase 3
NCT02439385	Not yet recruiting	Colorectal Cancer	Gachon University Gil Medical Center|Gachon University|Ajou Pharm	May 2015	Phase 2
NCT01740323	Recruiting	Breast Cancer	Andrew H Miller|Emory University	May 2015	Phase 2

Background

Challenges

- Nomenclature:
  - Turmeric, turmeric oil
  - Curcumin, curcuminoids
  - Standardized to x% curcumin

HydroCurcumin™

Product Description

HydroCurcumin™ is a solubilized curcumin product generated by the HydroParticle technology. It is easily dispersible in water, so it can be conveniently used for various types of foods including beverages. In case HydroCurcumin is used for dietary supplements it will enhance the bioavailability of curcumin.

Specification

Appearance	Yellow powder
Curcuminoid content	m.t. 20%
Loss on drying	n.m.t. 5%
Heavy metals	n.m.t. 10 ppm
Total microbial count	n.m.t. 1000 cfu/g
Yeast & mold	n.m.t. 100 cfu/g
Salmonella & E.Coli	Negative

Background

Adulteration

- Indian turmeric trade types curcumin contents ranging from 2.1% to 8.6%, with an average of 4.8%.
- *Curcuma longa* L. adulterated with wild species: *Curcuma zeodaria*, *Curcuma malabarica* – toxicity and poor quality
- Adulterated with artificial colors – metanyl yellow
- *Saffron is adulterated with turmeric*

Background

Challenges

- Clinical Phase I studies have shown that the blood serum levels of curcumin are in the ng/mL range after oral doses of up to 8 g of curcumin, suggesting very low gastro-intestinal bioavailability
- The reasons for the low oral bioavailability of curcumin are not yet known
  - chemical instability (degradation products are vanilin, ferulic acid, feruroyl methane)
  - rapid metabolism
  - poor absorption
  - accumulation in cells of the gastro-intestinal tract

Background

Analytical Needs

- Quantitative method for curcuminoids in
  - Raw material (plant material without authentication)
  - Extracts
  - Finished products containing only turmeric and/or curcuminoids
  - Finished products containing other ingredients (vitamins, other DS, herbs)
- Quantitative method for curcuminoids in
  - Capsules
  - Tablets
  - Tinctures
  - Softgel capsules

Background

Existing Methods

- SciFinder search: “turmeric and validation” and “2014-2015” yielded 97 references
- Spectrophotometric method for the estimation of curcumin in bulk and pharmaceutical formulation
- 1H-NMR and PCR for detecting *Curcuma longa* wild species adulterants
- HPLC and LC/MS are widely used analytical techniques

Workgroup meetings

Method Performance Requirements

- **High and low analytical range**
- **Reproducibility (RSDR)**
  - Original: ≤2%
  - Group discussion: ≤10%
  - After input from the industry members of the group: ≤3 and ≤6%
- **Repeatability (RSDr)**
  - Original: ≤1%
  - Group discussion: ≤5%
  - After input from the industry members of the group: ≤2 and ≤4%

Workgroup meetings

Dietary Supplement Label Database

(Supplement Facts Panel)

must include	*must include*	*products*	*"Rank"*	*must include*	*must include*	*products*	*"Rank"*
Turmeric		**809**		**Curcumin**		**300**	
	ginger	296	1		ginger	70	1, 2
	boswellia	88			boswellia	49	4
	MSM	82			MSM	28	
	glucosamine	85			glucosamine	26	
	chondroitin	48			chondroitin	16	
	Vitamin A	156	7		Vitamin A	47	6
	Vitamin B	194	3		Vitamin B	50	4
	Vitamin C	289	2		Vitamin C	70	1,2
	Vitamin D	159	6		Vitamin D	45	7
	Vitamin E	174	4		Vitamin E	44	
	Vitamin K	96			Vitamin K	19	
	pepper	164	5		pepper	56	3

Workgroup meetings

Other dietary ingredients

- *Piper nigrum*
- *Zingiber officinale*
- *Capsicum annuum*

Workgroup meetings

Dietary Supplement Ingredients Absorbing in the 400-450 nm Region

- α-carotene
- Antheraxanthin
- β-carotene
- β-cryptoxanthin
- Lutein
- Lycopene
- Riboflavin
- Riboflavin 5'-phosphate
- Violaxanthin
- Zeaxanthin

Workgroup meetings

Dietary Supplement Ingredients Absorbing in the 400-450 nm Region

- β-carotene
- Lutein
- Lycopene
- Zeaxanthin

- "For methods based on UV absorbance, all compounds in Table 2 must be evaluated for interference"

SMPR Key Points

- Reference method for cGMP compliance
- Quantitation of each individual curcuminoid and calculation of the sum of curcuminoids
- Method performance requirements:

Parameter	Requirement	
Limit of Quantitation (LOQ) (%)	≤ 0.1	
Recovery (%)	97 – 103	
Analytical Range (%)	≤ 0.1 – 50	> 50
% RSD_r	≤ 4	≤2
% RSD_R	≤ 6	≤ 3

SMPR Key Points

Possible Interferences

- *Piper nigrum*
- *Zingiber officinale* (ginger)
- *Capsicum annuum* (cayenne pepper)
- β-carotene
- Lutein
- Lycopene
- Zeaxanthin

SMPR Key Points

Matrices

- Dried plant material
- Extracts (purified curcuminoids)
- Tablets
- Capsules
- Softgel capsules
- Powders
- Tinctures
- Liquids

Comments Submitted

- 1 comment was submitted

  8. Validation Guidance:

     - Original text: For methods based on UV, all compounds in Table 2 must be evaluated for interference
     - Modification: For methods based on UV absorbance, all compounds in Table 2 must be evaluated for interference

- Minor editorial comments

Motion

- Move to accept the Standard Method Performance Requirements for Turmeric as presented.

Discussion?

DRAFT AOAC SMPR 2016.XXX; Version 6; November 25, 2015

Method Name: Quantitation of Curcuminoids

Intended Use: Reference method for cGMP compliance.

1. **Purpose:** AOAC SMPRs describe the minimum recommended performance characteristics to be used during the evaluation of a method. The evaluation may be an on-site verification, a single-laboratory validation, or a multi-site collaborative study. SMPRs are written and adopted by AOAC Stakeholder Panels composed of representatives from the industry, regulatory organizations, contract laboratories, test kit manufacturers, and academic institutions. AOAC SMPRs are used by AOAC Expert Review Panels in their evaluation of validation study data for method being considered for *Performance Tested Methods* or AOAC *Official Methods of Analysis*, and can be used as acceptance criteria for verification at user laboratories.

2. **Applicability**:
The method will be able to separate and quantify each individual curcuminoid, (curcumin, demethoxycurcumin, and bis-demethyoxycurcumin) in turmeric [*Curcuma longa* Linn.] dietary ingredients and dietary supplement finished products containing turmeric, alone or in combination with other dietary ingredients.

3. **Analytical Technique**:
Any analytical technique(s) that measures the analytes of interest and meets the following method performance requirements is/are acceptable.

4. **Definitions**:

Analytes

Curcumin
IUPAC name: (1*E*,6*E*)-1,7-Bis(4-hydroxy-3-methoxyphenyl)-1,6-heptadiene-3,5-dione. CAS registry number: 458-37-7. See figure 1 for molecular structure.

Demethoxycurcumin
IUPAC name: (1*E*,6*E*)-1-(4-Hydroxy-3-methoxyphenyl)-7-(4-hydroxyphenyl)hepta-1,6-diene-3,5-dione. CAS registry number: 24939-17-1. See figure 2 for the molecular structure of demethoxy-curcumin.

Bisdemethoxy-curcumin
IUPAC name: (1E,6E)-1,7-Bis(4-hydroxyphenyl)hepta-1,6-diene-3,5-dione. CAS registry number: 24939-16-0. See figure 3 for molecular structure.

Dietary Ingredients
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 total dietary intake; or a concentrate, metabolite, constituent, extract, or combination of any of the above dietary ingredients.[1]

[1] Federal Food Drug and Cosmetic Act §201(ff) [U.S.C. 321 (ff)

Dietary supplements

A product intended for ingestion that contains a "dietary ingredient" intended to add further nutritional value to (supplement) the diet. Dietary supplements may be found in many forms such as tablets, capsules, softgels, gelcaps, liquids, or powders.

Limit of Quantitation (LOQ)

The minimum concentration or mass of analyte in a given matrix that can be reported as a quantitative result.

Quantitative method

Method of analysis which response is the amount of the analyte measured either directly (enumeration in a mass or a volume), or indirectly (color, absorbance, impedance, etc.) in a certain amount of sample.

Repeatability

Variation arising when all efforts are made to keep conditions constant by using the same instrument and operator and repeating during a short time period. Expressed as the repeatability standard deviation (SD_r); or % repeatability relative standard deviation ($\%RSD_r$).

Reproducibility

The standard deviation or relative standard deviation calculated from among-laboratory data. Expressed as the reproducibility standard deviation (SD_R); or % reproducibility relative standard deviation (% RSD_R).

Recovery

The fraction or percentage of spiked analyte that is recovered when the test sample is analyzed using the entire method.

5. Method Performance Requirements:

See table 1.

6. System suitability tests and/or analytical quality control:

Suitable methods will include blank check samples, and check standards at the lowest point and midrange point of the analytical range.

7. Reference Material(s):

Curcumin USP Reference Standard (cat no.: 1151855)
Demethoxy-curcumin USP Reference Standard (cat no.: 1173100)
Bis-demethoxy-curcumin USP Reference Standard (cat no.: 1075305)
Curcuminoids USP Reference Standard (cat no.: 1151866)
NIST SRM 3299 Curcuma longa L. (Turmeric) Rhizome
NIST SRM 3300 Curcuma longa L. (Turmeric) Rhizome Extract

Refer to Annex F: *Development and Use of In-House Reference Materials* in Appendix F: *Guidelines for Standard Method Performance Requirements*, 19th Edition of the AOAC INTERNATIONAL Official Methods of Analysis (2012). Available at: http://www.eoma.aoac.org/app_f.pdf

8. Validation Guidance:

For methods based on UV, all compounds in Table 2 must be evaluated for interference.

Appendix D: Guidelines for Collaborative Study Procedures To Validate Characteristics of a Method of Analysis; 19th Edition of the AOAC INTERNATIONAL Official Methods of Analysis (2012). Available at: http://www.eoma.aoac.org/app_d.pdf

Appendix F: Guidelines for Standard Method Performance Requirements; 19th Edition of the AOAC INTERNATIONAL Official Methods of Analysis (2012). Available at: http://www.eoma.aoac.org/app_f.pdf

Appendix K: Guidelines for Dietary Supplements and Botanicals; 19th Edition of the AOAC INTERNATIONAL Official Methods of Analysis (2012). Available on line at: http://www.eoma.aoac.org/app_k.pdf

9. **Maximum Time-To-Result:** None

Table 1: Method performance requirements.

Parameter	Requirement	
Limit of Quantitation (LOQ) (%)	≤ 0.1	
Recovery (%)	97 – 103	
Analytical Range (%)	≤ 0.1 – 50	> 50
% RSD_r	≤ 4	≤2
% RSD_R	≤ 6	≤ 3

Table 2: Curcuminoids in the presence of other dietary ingredients, for example:

Piper nigrum
Zingiber officinale (ginger)
Capsicum annuum (cayenne pepper)
B-carotene
Lutein
Lycopene
Zeaxanthin

Table 3: Matrices

dried plant material
extracts (purified curcuminoids)
tablets
capsules
softgel capsules
powders
tinctures
liquids

Figure 1: Molecular structure of curcumin

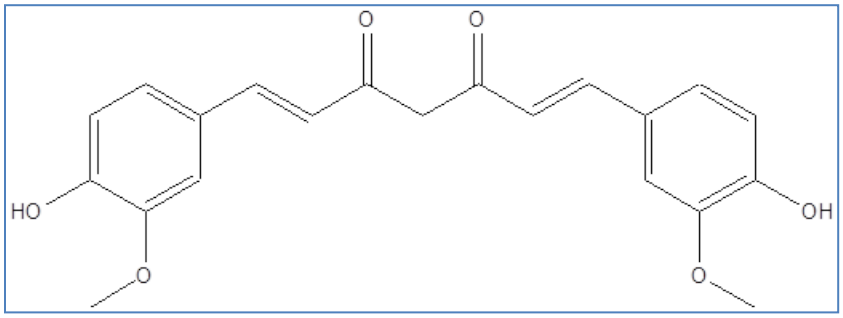


Figure 2: Molecular structure of demethoxycurcumin.

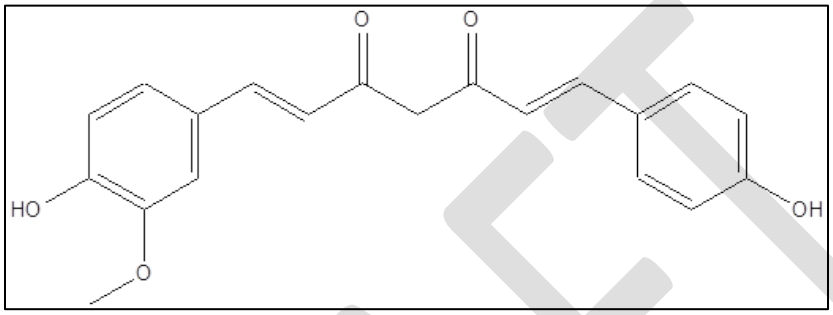
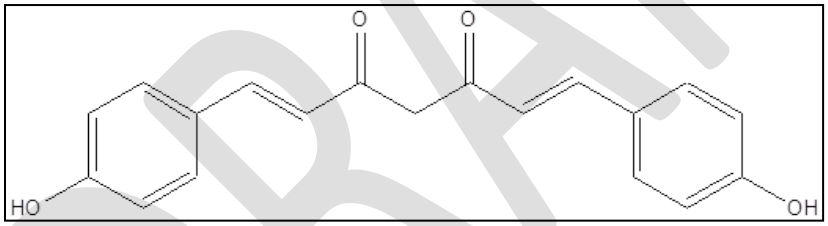


Figure 3: Molecular structure of bisdemethoxycurcumin



DRAFT

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STAKEHOLDER PANEL ON DIETARY SUPPLEMENTS

Background & Fitness for Purpose

Aloe vera

Kan He

AOAC 2016 Mid-Year Meeting

Gaithersburg, MD

March 17, 2016

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Background on Analyte

- Polysaccharides are one of the major constituents in *Aloe vera*.
- The major polysaccharide in aloe is glucomannan which is consisted of mannose (major) and glucose (minor) with 1,4-β-linked backbone. The mannose moieties are highly acetylated and are referred to Acemannan in literature.

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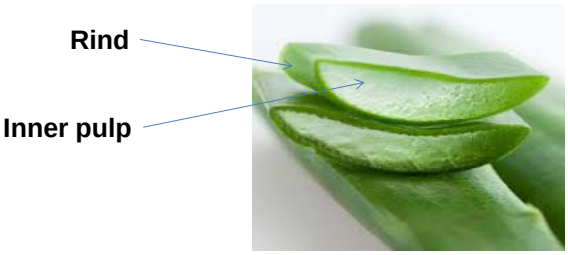
Background

- Aloe leaf consists of an outer green rind (skin) and an inner clear pulp;



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Background

- Both rind and inner pulp contain polysaccharides;
- Other major components in aloe leaf are organic acids, minerals, and monosaccharides;
- Rind contains four major organic acids, malate, isocitrate, isocitrate lactone, and citrate, while pulp contains major malate and some citrate, but very minimal isocitrate and isocitrate lactone;

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Background

- Based on the parts to be used, aloe leaf products can be divided into:
  - Entire leaf juice;
  - Inner leaf juice;
- Based on manufacturing process, aloe products can be divided into:
  - Enzymatic treatment;
  - Non-enzymatic treatment;

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Background

- Accepted criteria by aloe industry, the average solid contents in the inner gel are about 0.5% and entire leaf 1%.
- The concentration of aloe product is expressed:
  - 5X: 5 Time concentrated comparing with fresh aloe leaf;
  - 200X: Inner leaf extract (200 parts of inner gel to make 1 part of powder);
  - 100X: entire leaf extract (100 parts of entire leaf to make 1 part of powder) or 200X is diluted with 50% excipients;

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Significance

- Acemannan is reported to be response to biological activities of *Aloe vera* including:
  - Immunostimulatory;
  - Anti-inflammatory;
  - Hypoglycemic and hypolipidemic activities;
  - Antibacterial, antiviral, and antitumor effects;

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General Analytical Needs

- Method should:
  - Qualitatively identify aloe polysaccharides;
  - Quantitatively determine aloe polysaccharide contents;
  - Determine molecular weight of aloe polysaccharides;
  - Differentiate aloe product type, entire leaf vs. inner leaf;

Challenges

- A single method to meet all the requirements;
- Exclusive to aloe polysaccharides;
- Accurately quantitate aloe polysaccharides;
- Discrepancies of aloe polysaccharide structures reported in literature;

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Existing Methods - General

- HPTLC
- Colorimetric Assay by Red Dye
- Colorimetric Assay of Acetyl Groups of Polysaccharides
- ^{1}H NMR Spectroscopic Method
- Size Exclusion Chromatography

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Existing Methods

- HPTLC
  - Lobo *et al*., A HPTLC densitometric method for the determination of aloeverose in *Aloe vera* gel. *Fitoterapia* **2010**, *81,* 231–233.

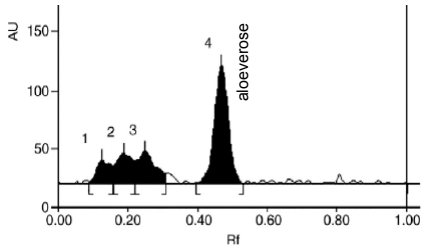

Fig. HPTLC chromatogram of *A. vera* gel (from the above paper).

HPTLC conditions:
Plate: Si-gel Si60F_{254}
Developing: n-butanol: n-propanol: glacial acetic acid: water (30:10:10:10 v/v/v/v).
Reagents: anisaldehyde sulphuric acid reagent; heating the plate at 105–110°C for 5min.

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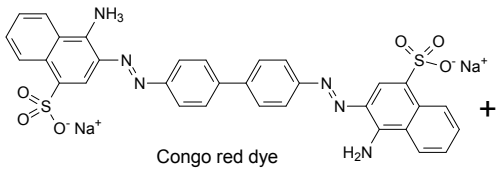
Existing Methods

- Colorimetric Assay by Red Dye – Congo Red
  - Eberendu *et al*., Quantitative Colorimetric Analysis of Aloe Polysaccharides as a Measure of *Aloe Vera* Quality in Commercial Products. *J. AOAC International*, **2005**, *88*, 684-691.



Congo red dye

+ Aloe polysaccharides

- Complex of Congo red with polysaccharides and assayed at 540nm

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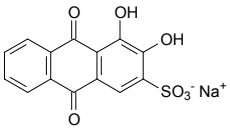
Existing Methods

- Colorimetric Assay by Red Dye – Alizarin Red
  - Gu *et al*., Binding interaction between aloe polysaccharide and alizarin red by spectrophotometry and its analytical application. *Carbohydrate Polymers.* **2010**, *80*, 115–122.



alizarin red

+ Aloe polysaccharides

- Complex of alizarin red with polysaccharides and assayed at 325nm and 516nm

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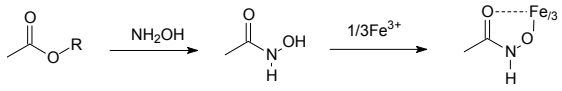
Existing Methods

- Colorimetric Assay of Acetyl Groups of Polysaccharides
  - Aloe Products for Food Raw Material, Chinese National Standard, QB/T 2489 2007



Acetohydroxamic Acid Ferric-Acethydroxamic Acid Complex

- The acetyl groups on polysaccharides are reacted with hydroxylamine to form acetohydroxamic acid. The resulted acetohydroxamic acid is reacted with ferric trichloride to form a ferric-acethydroxamic acid complex and measured 540nm.

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Existing Methods

- ^{1}H NMR Spectroscopic Method
  - B. Diehl & E. E. Teichmuller, *Aloe vera*, Quality and Identification, *SOFW-Journal* **1997**, *123*, Jahrgang, 1015-1018.
  - Bozzi *et al*., Quality and authenticity of commercial aloe vera gel powders. *Food Chem*., **2007**, 103, 22-30.
  - B. Davis & W. J. Goux, Single-Laboratory Validation of an NMR Method for the Determination of Aloe Vera Polysaccharide in Pharmaceutical Formulations, *J. of AOAC International.* **2009**, *92*, 1607-1616.
  - Jiao *et al*. Quantitative ^{1}H-NMR Spectrometry Method for Quality Control of *Aloe vera* Products. *J. of AOAC International*, **2010**, *93*, 842-847.
  - J. Edwards in *Aloe Vera Leaf, Aloe Vera Leaf Juice, and Aloe Vera Inner leaf Juice, Aloe vera (L.) Burm. f. Standards of Identity, Analysis, and Quality Control*. R. Upton *et al*. Eds. *American Herbal Pharmacopeia* 2012, pp 33-42.

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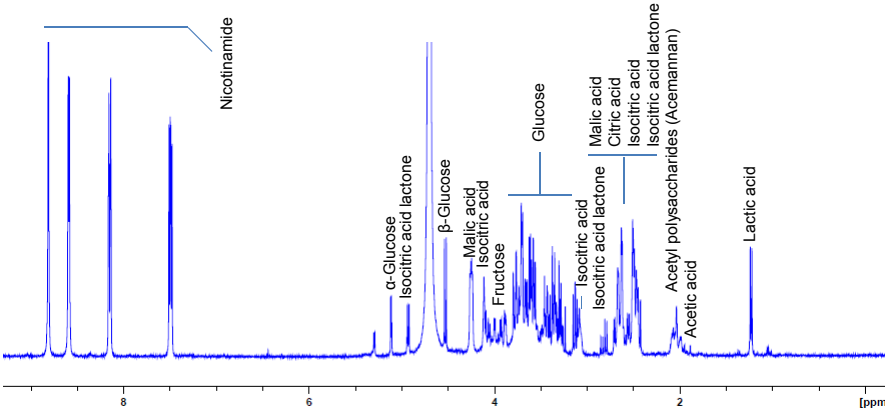
Existing Methods

- ^{1}H NMR Spectroscopic Method



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Existing Methods

- Size Exclusion Chromatography
  - Turner *et al*. Evaluation and comparison of commercially available *Aloe vera* L. products using size exclusion chromatography with refractive index and multi-angle laser light scattering detection. *International Immunopharmacology*. **2004**, *4*, 1727–1737.

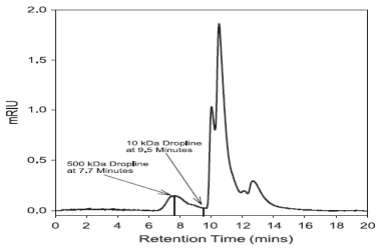

Fig. is from the above paper

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Regulatory Guidance

- No information regarding the determination of aloe acetyl polysaccharide contents in the following pharmacopoeias:
  - United States Pharmacopeia;
  - European Pharmacopoeia
  - Chinese Pharmacopoeia;
  - Japanese Pharmacopoeia;

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Fitness for Purpose (proposal)

- The methods are able to qualitatively identify aloe vera;
- Are able to accurately quantitate not only the contents of aloe polysaccharides, but also the molecular weight;
- Are able to accurately quantitate the aloe polysaccharides with different molecular weight;

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QUESTIONS??

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STAKEHOLDER PANEL ON Dietary Supplements

Background & Fitness for Purpose

Protein

Spencer Carter

AOAC 2016 Mid-Year Meeting

Gaithersburg, MD

17 March 2016

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Outline

- Background
- Significance
- Adulteration
- Existing Methods
  - Qualitative
  - Quantitative
- Challenges with Existing Methods
- Things to Consider
- Fitness for Purpose (proposal)
- Questions

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Background

- Proteins are polypetides made of individual amino acids in a linear chain
- Form the basis of life and perform functions in every system of the human body
    - Enzymes catalyze biochemical reactions
    - Hormones are used for cell signaling and communication
    - Synthesize and repair DNA
    - Tranport materials across the cell
    - Respond to stimuli
    - Provide structural support

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Significance

- Estimated that 4 billion metric tons of food protein is produced globally
- Estimated that $94M was lost by changing the nitrogen-to-protein factor for dairy products from 6.38 to 6.25 in Europe in 2006
- Proteins make up $4.7B dollars in the Sports Nutrition industry, which represents 70% of the total revenue in that category

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Adulteration

- Non-selective protein methods have fueled the potential to adulterate samples with non-proteins and give inaccurate results
- Melamine, urea, free amino acids cannot be differentiated using Kjeldahl, Dumas methods and have been the source of scandals
- Public health is still at risk; Economics still push adulteration

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Existing Methods (Qualitative)

- Some proteins have FCC monographs. For example, Whey Protein is identified by testing for:
  - Ash
  - Fat
  - Lactose
  - Loss on drying
  - Nitrogen (and apply conversion factor)
- DNA Analysis
- LC/MS/MS

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Existing Methods (Quantitative)

- Kjeldahl
  1. Wet digestion converts nitrogen to ammonium sulfate
  2. Neutralize to convert to free ammonia
  3. Distill ammonia into boric acid
  4. Back titrate with alkali
  5. Convert nitrogen concentration to protein using conversion ratio
  - "True Protein" can be determined by precipitating out protein, analyzing remaining nitrogen, subtracting from total nitrogen content

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Existing Methods (con't)

- Dumas
  1. Combust samples at high temp with oxygen to form water, carbon dioxide, nitrogen
  2. Remove water and carbon dioxide using column
  3. Nitrogen is measured using a thermal conductivity detector
  4. Convert nitrogen concentration to protein using conversion ratio

Existing Methods (con't)

- Amino Acids
  1. Hydrolyze protein into amino acids
  2. Derivatize amino acids
  3. Determine protein by summing individual amino acids
- Dye-binding
  1. Form complex with dye and protein using ionic or electrostatic forces.
  2. Determine dye concentration using spectrophotometer

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Existing Methods (con't)

- Copper-Binding
  1. Copper ions react with proteins to form complex
  2. Measure absorbance at 540 nm
- Others
  - UV absorption
  - Infrared

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Challenges with Existing Methods

- Kjeldahl, Dumas: not selective to protein;
- True Protein Kjeldahl: non-protein, nitrogen-containing compounds may precipitate or form complex with precipitated protein
- Amino Acid: Inaccurate quantitation due to variable recovery of amino acids
- Copper, Dye-Binding: other constituents besides proteins form complexes
- Lack of Standards
  - Protein biosynthesis is expensive, time-consuming, not robust
  - Proteins samples vary widely and usually include multiple proteins

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Things to Consider

- Should method address qualitative or quantitative aspect? Or, both?
- Should ranges be established for quantitative methods?
- Are multiple methods required as part of orthogonal approach due to complex nature?
- How to define which proteins need to be analyzed, since samples usually contain multiple proteins, and even the same protein species can be diverse between samples?
- How to overcome the challenge of obtaining adequate reference material standards?

Fitness for Purpose (proposal)

- Qualitative method must provide positive confirmation of specific protein. Quantitative method must provide accurate and precise concentrations of specific proteins in raw materials and finished goods. Orthogonal methods may be required due to complex approach to analysis.

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QUESTIONS??

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STAKE HOLDER PANEL FOR DIETARY SUPPLEMENTS

Background and Fitness for Purpose

Vitamin B12

Richard B. van Breemen, Ph.D.
Gaithersburg, MD
March 17, 2016

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Background on Vitamin B12

- Recognized as a fatal disease over 100 years ago, vitamin B12 deficiency causes megaloblastic anemia as well as neurological abnormalities.
- Development of effective dietary supplement therapy for “pernicious” anemia resulted in a Nobel Prize for Minot, Murphy and Whipple in 1934.
- Dorothy Hodgkin received a Nobel Prize in 1964 for her X-ray crystallographic structure determination of vitamin B12.

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Background on Vitamin B12

- Vitamin B12 (cobalamin) is a group water soluble corrinoids with a cobalt-coordinated nucleotide containing the base, 5,6-dimethylbenzimidazole.
- Vitamin B12 is synthesized only in certain bacteria and becomes concentrated in higher organisms along the food chain.
- Therefore, animal-based foods are the primary sources of vitamin B12 in the human diet.
- Vegans and people with digestive insufficiencies are at greatest risk of vitamin B12 deficiency.

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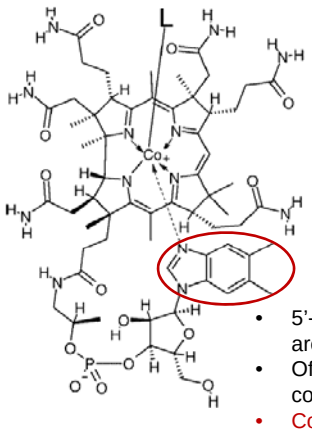
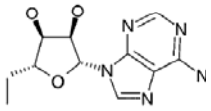
Vitamin B12 and Related Cobalamins



L=

5'-Deoxyadenosylcobalamin



-CH_3 Methylcobalamin

-OH Hydroxocobalamin

-SO_3 Sulfitocobalamin

-CN Cyanocobalamin

- 5'-Deoxyadenosylcobalamin and methylcobalamin are physiologically active
- Often used in dietary supplements, other cobalamins can be converted in vivo
- Corrinoids containing bases other than 5,6-dimethylbenzimidazole are inactive

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General Analytical Needs

- Method should
  - measure the physiologically active vitamin B12 compounds
    - 5'-deoxyadenosylcobalamin and methylcobalamin
  - measure the provitamin B12 forms
    - Including hydroxocobalamin, sulfitocobalamin and cyanocobalamin (which is the form most often used in dietary supplements)
  - distinguish between vitamin B12 active corrinoids containing the base, 5,6-dimethylbenzimidazole and inactive forms present in some dietary supplements (especially those derived from edible cyanobacteria).

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Analytical Challenges

- Quantitatively extract vitamin B12 compounds from a variety of matrices including finished products such as capsules and pills and unprocessed raw materials such as cyanobacteria.
- Measurement of trace levels of vitamin B12 compounds in natural sources as well as in fortified samples.
- Measure multiple vitamin B12 compounds individually or after derivatization to a common form such as cyanocobalamin.
- Distinguish vitamin B12 cobalamins from inactive forms.

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Regulations

- Intake recommendations for vitamin B12 are provided in the Dietary Reference Intakes (DRIs) developed by the Food and Nutrition Board (FNB) at the Institute of Medicine (IOM) of the National Academies (formerly National Academy of Sciences).
- For healthy adult men and women (not pregnant or lactating), the recommended daily allowance is 2.4 µg.
- RDAs for other ages: 0–6 mos 0.4 µg; 7–12 mos 0.5 µg; 1–3 yr 0.9 µg; 4–8 yr 1.2 µg; 9–13 yr 1.8 µg; 14+ yr 2.4 µg
- Prescription injectable (*im*), intranasal and parenteral forms of vitamin B12 are available.

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Current Analytical Methods for Vitamin B12

- Bioassay using vitamin B12 dependent bacteria, such as *Lactobacillus delbrueckii* subsp. *lactis* ATCC7830
- Radioimmunoassay (RIA) and radioisotope dilution assays using radioactive ^{57}Co & binding protein (intrinsic factor)
- Chemiluminescence using acridinium ester-labeled vitamin B12 and intrinsic factor
- Surface plasmon resonance of prepared samples
- HPLC-UV following immunoaffinity extraction
- HPLC-UV following solid phase extraction, with or without derivatization (conversion) to cyanocobalamin
- HPLC-MS and HPLC-MS/MS

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Existing Methods for Vitamin B12

- USP – cyanocobalamin and hydroxocobalamin pure substances and injectable solutions, tablets and capsules by spectrophotometry and HPLC-UV
- AOAC International
  - 952.20 vitamin preparations by microbiological assay
  - 986.23 milk-based infant formula by microbiological assay
  - 2011.08 and 2011.09 infant formula and adult nutritionals by HPLC-UV with immunoaffinity extraction after conversion to cyanocobalamin (first action)
  - 2011.10 infant formula and adult nutritionals by HPLC-UV with column switching after solid phase extraction
  - 2011.16 infant formula and adult nutritionals by surface plasmon resonance

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Fitness for Purpose (proposal)

The method for vitamin B12 dietary supplement analysis must quantitate multiple forms of vitamin B12 individually or after conversion to a common form (such as the more stable cyanocobalamin) in a variety of dosage forms. The method must also be able to distinguish between active vitamin B12 corrinoids and inactive forms present in products derived from some microbiological sources. As humans can only absorb 10 to 500 µg B12/day and the RDA is from 0.4 to 2.8 µg B12/day, the analytical range for supplements should extend from at least 0.1 to 1000 ppm per dosage unit.

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QUESTIONS?

SPDS
2016 AOAC MIDYEAR MEETING, MARCH 17-18
STAKEHOLDER PANEL ON DIETARY SUPPLEMENTS

RESOURCES

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Useful Web Links:

AOAC Website: http://www.aoac.org

SPDS Microsite: http://bit.ly/1rU4BmU

SPDS Standards Development: Working Group Sign Up: https://form.jotform.com/60285694384163

SPDS Conformity Assessment: Call for Experts / ERP Application: http://tinyurl.com/zrv7ro7

SPDS Conformity Assessment: Set 3 Ingredient Call for Methods: http://tinyurl.com/oh8n54w

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Not on the list? Email SPDS@aoac.org to be added so you don't miss any of the latest updates!

Stakeholder Panel on Dietary Supplements

As of: March 11, 2016

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Appendix W

POLICY AND PROCEDURES ON VOLUNTEER CONFLICT OF INTEREST

Statement of Policy

While it is not the intention of AOAC INTERNATIONAL (AOAC) to restrict the personal, professional, or proprietary activities of AOAC members nor to preclude or restrict participation in Association affairs solely by reason of such activities, it is the sense of AOAC that conflicts of interest or even the appearance of conflicts of interest on the part of AOAC volunteers should be avoided. Where this is not possible or practical under the circumstances, there shall be written disclosure by the volunteers of actual or potential conflicts of interest in order to ensure the credibility and integrity of AOAC. Such written disclosure shall be made to any individual or group within the Association which is reviewing a recommendation which the volunteer had a part in formulating and in which the volunteer has a material interest causing an actual or potential conflict of interest.

AOAC requires disclosure of actual or potential conflicts of interest as a condition of active participation in the business of the Association. The burden of disclosure of conflicts of interest or the appearance of conflicts of interest falls upon the volunteer.

A disclosed conflict of interest will not in itself bar an AOAC member from participation in Association activities, but a three-fourths majority of the AOAC group reviewing the issue presenting the conflict must concur by secret ballot that the volunteer's continued participation is necessary and will not unreasonably jeopardize the integrity of the decision-making process.

Employees of AOAC are governed by the provision of the AOAC policy on conflict of interest by staff. If that policy is in disagreement with or mute on matters covered by this policy, the provisions of this policy shall prevail and apply to staff as well.

Illustrations of Conflicts of Interest

1. A volunteer who is serving as a committee member or referee engaged in the evaluation of a method or device; who is also an employee of or receiving a fee from the firm which is manufacturing or distributing the method or device or is an employee of or receiving a fee from a competing firm.

2. A volunteer who is requested to evaluate a proposed method or a related collaborative study in which data are presented that appear detrimental (or favorable) to a product distributed or a position supported by the volunteer's employer.

3. A referee who is conducting a study and evaluating the results of an instrument, a kit, or a piece of equipment which will be provided gratis by the manufacturer or distributor to one or more of the participating laboratories, including his or her own laboratory, at the conclusion of the study.

4. Sponsorship of a collaborative study by an interest (which may include the referee) which stands to profit from the results; such sponsorship usually involving the privilege granted by the investigator to permit the sponsor to review and comment upon the results prior to AOAC evaluation.

5. A volunteer asked to review a manuscript submitted for publication when the manuscript contains information which is critical of a proprietary or other interest of the reviewer.

The foregoing are intended as illustrative and should not be interpreted to be all-inclusive examples of conflicts of interest AOAC volunteers may find themselves involved in.

Do's and Don't's

Do avoid the appearance as well as the fact of a conflict of interest.

Do make written disclosure of any material interest which may constitute a conflict of interest or the appearance of a conflict of interest.

Do not accept payment or gifts for services rendered as a volunteer of the Association without disclosing such payment or gifts.

Do not vote on any issue before an AOAC decision-making body where you have the appearance of or an actual conflict of interest regarding the recommendation or decision before that body.

Do not participate in an AOAC decision-making body without written disclosure of actual or potential conflicts of interest in the issues before that body.

Do not accept a position of responsibility as an AOAC volunteer, without disclosure, where the discharge of the accepted responsibility will be or may appear to be influenced by proprietary or other conflicting interests.

Procedures

Each volunteer elected or appointed to an AOAC position of responsibility shall be sent, at the time of election or appointment, a copy of this policy and shall be advised of the requirement to adhere to the provisions herein as a condition for active participation in the business of the Association. Each volunteer, at the time of his or her election or appointment, shall indicate, in writing, on a form provided for this purpose by AOAC, that he or she has read and accepts this policy.

Each year, at the spring meeting of the AOAC Board of Directors, the Executive Director shall submit a report certifying the requirements of this policy have been met; including the names and positions of any elected or appointed volunteers who have not at that time indicated in writing that they have accepted the policy.

Anyone with knowledge of specific instances in which the provisions of this policy have not been complied with shall report these instances to the Board of Directors, via the Office of the Executive Director, as soon as discovered.

* * * * * *

Adopted: March 2, 1989
Revised: March 28, 1990
Revised: October 1996
Reviewed by outside counsel March 2000 (Fran Dwornik) and found to be current and relevant

Appendix U

ANTITRUST POLICY STATEMENT AND GUIDELINES

Introduction

It is the policy of AOAC INTERNATIONAL (AOAC) and its members to comply strictly with all laws applicable to AOAC activities. Because AOAC activities frequently involve cooperative undertakings and meetings where competitors may be present, it is important to emphasize the on-going commitment of our members and the Association to full compliance with national and other antitrust laws. This statement is a reminder of that commitment and should be used as a general guide for AOAC and related individual activities and meetings.

Responsibility for Antitrust Compliance

The Association's structure is fashioned and its programs are carried out in conformance with antitrust standards. However, an equal responsibility for antitrust compliance -- which includes avoidance of even an appearance of improper activity -- belongs to the individual. Even the appearance of improper activity must be avoided because the courts have taken the position that actual proof of misconduct is not required under the law. All that is required is whether misconduct can be inferred from the individual's activities.

Employers and AOAC depend on individual good judgment to avoid all discussions and activities which may involve improper subject matter and improper procedures. AOAC staff members work conscientiously to avoid subject matter or discussion which may have unintended implications, and counsel for the Association can provide guidance with regard to these matters. It is important for the individual to realize, however, that the competitive significance of a particular conduct or communication probably is evident only to the individual who is directly involved in such matters.

Antitrust Guidelines

In general, the U.S. antitrust laws seek to preserve a free, competitive economy and trade in the United States and in commerce with foreign countries. Laws in other countries have similar objectives. Competitors (including individuals) may not restrain competition among themselves with reference to the price, quality, or distribution of their products, and they may not act in concert to restrict the competitive capabilities or opportunities of competitors, suppliers, or customers.

Although the Justice Department and Federal Trade Commission generally enforce the U.S. antitrust laws, private parties can bring their own lawsuits. Penalties for violating the U.S. and other antitrust laws are severe: corporations are subject to heavy fines and injunctive decrees, and may have to pay substantial damage judgments to injured competitors, suppliers, or customers. Individuals are subject to criminal prosecution, and will be punished by fines and imprisonment. Under current U.S. federal sentencing guidelines, individuals found guilty of bid rigging, price fixing, or market allocation must be sent to jail for at least 4 to 10 months and must pay substantial minimum fines.

Since the individual has an important responsibility in ensuring antitrust compliance in AOAC activities, everyone should read and heed the following guidelines.

1. Don't make any effort to bring about or prevent the standardization of any method or product for the purpose or intent of preventing the manufacture or sale of any method or product not conforming to a specified standard
2. Don't discuss with competitors your own or the competitors' prices, or anything that might

affect prices such as costs, discounts, terms of sale, distribution, volume of production, profit margins, territories, or customers.

3. Don't make announcements or statements at AOAC functions, outside leased exhibit space, about your own prices or those of competitors.

4. Don't disclose to others at meetings or otherwise any competitively sensitive information.

5. Don't attempt to use the Association to restrict the economic activities of any firm or any individual.

6. Don't stay at a meeting where any such price or anti-competitive talk occurs.

7. Do conduct all AOAC business meetings in accordance with AOAC rules. These rules require that an AOAC staff member be present or available, the meeting be conducted by a knowledgeable chair, the agenda be followed, and minutes be kept.

8. Do confer with counsel before raising any topic or making any statement with competitive ramifications.

9. Do send copies of meeting minutes and all AOAC-related correspondence to the staff member involved in the activity.

10. Do alert the AOAC staff to any inaccuracies in proposed or existing methods and statements issued, or to be issued, by AOAC and to any conduct not in conformance with these guidelines.

Conclusion

Compliance with these guidelines involves not only avoidance of antitrust violations, but avoidance of any behavior which might be so construed. Bear in mind, however, that the above antitrust laws are stated in general terms, and that this statement is not a summary of applicable laws. It is intended only to highlight and emphasize the principal antitrust standards which are relevant to AOAC programs. You must, therefore, seek the guidance of either AOAC counsel or your own counsel if antitrust questions arise.

Adopted by the AOAC Board of Directors: September 24, 1989
Revised: March 11, 1991
Revised October 1996

Appendix V

POLICY ON THE USE OF THE ASSOCIATION NAME, INITIALS, IDENTIFYING INSIGNIA, LETTERHEAD, AND BUSINESS CARDS

Introduction

The following policy and guidelines for the use of the name, initials, and other identifying insignia of AOAC INTERNATIONAL have been developed in order to protect the reputation, image, legal integrity and property of the Association.

The name of the Association, as stated in its bylaws, is "AOAC INTERNATIONAL". The Association is also known by its initials, AOAC, and by its logo, illustrated below, which incorporates the Association name and a representation of a microscope, book, and flask. The AOAC logo is owned by the Association and is registered with the U.S. Patent and Trademark Office.

The full Association insignia, illustrated below, is comprised of the logo and the tagline, "The Scientific Association Dedicated to Analytical Excellence," shown below. The typeface used is Largo. The AOAC tagline is owned by the Association and is registered with the U.S. Patent and Trademark office.

The Scientific Association Dedicated to Analytical Excellence®

Policy

Policy on the use of the Association's name and logo is established by the AOAC Board of Directors as follows:

> "The Board approves and encourages reference to the Association by name, either as AOAC INTERNATIONAL or as AOAC; or reference to our registered trademark, AOAC®, in appropriate settings to describe our programs, products, etc., in scientific literature and other instances so long as the reference is fair, accurate, complete and truthful and does not indicate or imply unauthorized endorsement of any kind.
>
> The insignia (logo) of AOAC INTERNATIONAL is a registered trade and service mark and shall not be reproduced or used by any person or organization other than the Association, its elected and appointed officers, sections, or committees, without the prior written permission of the Association. Those authorized to use the AOAC INTERNATIONAL insignia shall use it only for

the purposes for which permission has been specifically granted.

The name and insignia of the Association shall not be used by any person or organization in any way which indicates, tends to indicate, or implies AOAC official endorsement of any product, service, program, company, organization, event or person, endorsement of which, has not been authorized by the Association, or which suggests that membership in the Association is available to any organization."

The Executive Director, in accordance with the above stated policy, is authorized to process, approve, fix rules, and make available materials containing the Association name and insignia.

It should be noted that neither the Association's name nor its insignia nor part of its insignia may be incorporated into any personal, company, organization, or any other stationery other than that of the Association; nor may any statement be included in the printed portion of such stationery which states or implies that an individual, company, or other organization is a member of the Association.

Instructions

1. Reproduction or use of the Association name or insignia requires prior approval by the Executive Director or his designate.

2. Association insignia should not be altered in any manner without approval of the Executive Director or his designate, except to be enlarged or reduced in their entirety.

3. Artwork for reproducing the Association name or insignia, including those incorporating approved alterations, will be provided on request to those authorized to use them (make such requests to the AOAC Marketing Department). Examples of the types of alterations that would be approved are inclusion of a section name in or the addition of an officer's name and address to the letterhead insignia.

4. When the Association name is used without other text as a heading, it should, when possible, be set in the Largo typeface.

5. Although other colors may be used, AOAC blue, PMS 287, is the preferred color when printing the AOAC insignia, especially in formal and official documents. It is, of course, often necessary and acceptable to reproduce the insignia in black.

6. Do not print one part of the logo or insignia in one color and other parts in another color.

7. The letterhead of AOAC INTERNATIONAL shall not be used by any person or organization other than the Association, elected and appointed officers, staff, sections, or committees; except by special permission.

   Correspondence of AOAC official business should be conducted using AOAC letterhead. However, those authorized to use AOAC letterhead shall use it for official AOAC business only.

   Copies of all correspondence using AOAC letterhead or conducting AOAC official business,

whether on AOAC letterhead or not, must be sent to the appropriate office at AOAC headquarters.

8. AOAC INTERNATIONAL business cards shall not be used by any person or organization other than the Association, its staff, and elected officials, except by special permission.

   Those authorized to use AOAC business cards shall use them for official AOAC business only and shall not represent themselves as having authority to bind the Association beyond that authorized.

Sanctions

1. Upon learning of any violation of the above policy, the Executive Director or a designate will notify the individual or organization that they are in violation of AOAC policy and will ask them to refrain from further misuse of the AOAC name or insignia.

2. If the misuse is by an Individual Member or Sustaining Member of the Association, and the misuse continues after notification, the Board of Directors will take appropriate action.

3. If continued misuse is by a nonmember of the Association or if a member continues misuse in spite of notification and Board action, ultimately, the Association will take legal action to protect its property, legal integrity, reputation, and image.

* * * * * *

Adopted by the AOAC Board of Directors: September 24, 1989
Revised: June 13, 1991; February 26, 1992; March 21, 1995; October 1996

AOAC Stakeholder Panel Voting Members

AOAC INTERNATIONAL (AOAC) assembles stakeholder panels to develop voluntary consensus standards. While AOAC maintains transparency and openness in accordance with national and international guidance and regulations for standards development and its policies and procedures for assembling stakeholder panels, its policies and procedures also ensures that there is a balance of interests and perspectives in achieving consensus of the stakeholder panel.

Due Process and Balance

All AOAC stakeholder panels are diverse and can vary in size. Where a stakeholder panel is not balanced or if it is significantly large whereby consensus of the general assembly may be impractical, a balanced representative voting panel will be used to demonstrate consensus. AOAC encourages ALL stakeholders to participate in deliberations during stakeholder panel meetings and working group meetings, in addition to participating during any posted comment periods. To ensure that there is a balance of interests and perspectives, a ***representative subset*** of the stakeholder panel, the voting members, is selected to reach consensus for the development of AOAC voluntary consensus standards.

Composition

Voting members represent the perspectives of the larger stakeholder panel. The voting members consist of no more than ¼ to 1/3 of the total number of stakeholders in registered. Primary and secondary representative voting members are approved. Every attempt is made to approve a panel of voting members that represents all perspectives of the stakeholder panel. In the event of a primary voting member is not able to attend, and no alternate has been approved, the stakeholder panel chair, working with AOAC can provisionally approve an alternate from those in attendance to assure balance and lack of dominance. For stakeholder panels with scopes including diverse topics, the voting member representatives may be rotated to include other stakeholders for successive meetings to ensure a lack of dominance by any particular stakeholder.

Approval Process

AOAC works with the chair of the stakeholder panel and potentially other key stakeholders to develop a proposed representative voting member panel. Following AOAC policies and procedures, the proposed voting members and documentation are submitted to the AOAC Official Methods Board (OMB) for review and approval. The OMB's review ensures that the proposed panel is balanced in interests and perspectives representing the stakeholder panel and a lack of dominance.

Roles and Responsibilities

Every stakeholder has a voice and every stakeholder is entitled to state his/her or organizational perspective(s). This is due process. In developing AOAC standards, stakeholder consensus is demonstrated by 2/3 vote (67%) in favor of a motion to adopt a standard. It is important to note: Individual voting members do not have any additional weight, voice or status in stakeholder deliberations than other stakeholders. The role of the voting members is to demonstrate the consensus of the stakeholder panel. Voting members may vote in favor or against any motion and/or they may abstain. Stakeholder panel chair will moderate voting process. AOAC carefully documents the vote. It is important for voting members to be in the room during the time for voting. It is also important for voting members to inform the chair of his/her inability to serve as a voting member.

AOAC INTERNATIONAL

STAKEHOLDER PANEL ON DIETARY SUPPLEMENTS (SPDS)
WORKING GROUP CHAIR & MEMBERS

VOLUNTEER ROLE DESCRIPTION

POSITION TITLE: **Working Group Chair and Members, AOAC SPDS Working Group**
POSITION CLASSIFICATION: **Volunteer**
REPORTS TO: **SPDS Chair**
DATE PREPARED: **March 13, 2014**

POSITION SUMMARY:
In keeping with the mission of AOAC INTERNATIONAL and the goals of the Stakeholder Panel on Dietary Supplements (SPDS), working group chairs will lead their working group in the development of standards (or other tasks as assigned by the SPDS chair) for specific priority ingredients as defined by the SPDS Advisory Panel. Working group chair(s) will work with AOAC staff and stakeholders to meet the working group's goals and disseminate recommendations to the stakeholder panel and community at-large. The working group may hold meetings in person and/or via teleconference (web and video) to complete its work. The chair of the working group will moderate the working group discussions, assist in scheduling the meetings, and report the working group's recommendation back to SPDS. Working group chairs will work with AOAC to formulate the working group's recommendations into motions for SPDS's consideration.

ELIGIBILITY CRITERIA FOR SPDS WORKING GROUP CHAIR:
- Must be a key expert and/or thought leader in dietary supplements and the technologies used for priority ingredients as assigned for the specific working group.
- Must have the recommendation of the SPDS Chair.

WORKING GROUP CHAIR RESPONSIBILITIES:
- Chair meetings of the working group, moderate discussions of the working group and work with AOAC staff to facilitate working group's work.
- Work with AOAC staff and SPDS chair to identify working group members, any additional expertise/resources needed facilitate the work of the working group.
- Work as a team member and also independently.
- Present an overview on the specified priority ingredient under consideration including, but not limited to, regulatory implications, and public health and public safety challenges with methodology.
- Prepare a draft fitness for purpose statement for specified priority ingredient and technology to present to SPDS for consideration.
- Work with AOAC staff to reconcile actions and outcomes of working group deliberations.
- Using AOAC guidance to reconcile comments and address questions on SMPR.
- Present working group recommended SMPR to SPDS for review and approval.
- Work with AOAC staff and stakeholders to draft and review relevant methodology and working group documentation.
- Draft SMPR white paper for publication.
- Perform duties and reviews in timely fashion.
- Other tasks as agreed upon by working group chair, SPDS chair and AOAC staff.

DUTIES AND RESPONSIBILITIES OF THE SPDS WORKING GROUP MEMBERS:
The working group will meet either in person and via teleconference, web conferencing or by other means of communication. All communication and meetings of the working group must be facilitated through AOAC

staff. The working group's tasks will include developing standard method performance requirements (SMPRs), review of methodology, identifying expertise and other as may be requested by the SPDS chair. Working groups are not required to vote, but to show general consensus for its recommendations. The groups should meet to discuss their objectives and complete their assigned tasks. Individuals on the working groups may be tasked with their own action items and responsibilities. More than one meeting and one round of communication may be required to complete the working group's tasks. All working group participants are expected to contribute and are expected to have completed the SMPR Education Session. AOAC staff will document all working group decisions and actions.

AOAC RESOURCES:

- Referencing AOAC guidance documentation to assist in drafting the fitness for purpose statement, standard method performance requirements (SMPR), and additional work as tasked.
    1) AOAC Fitness for Purpose Statement Guideline
    2) Appendix F: Guidelines for Standard Method Performance Requirements
    3) Appendix K: Guidelines for Dietary Supplements and Botanicals

STAFF LIASON:

AOAC will assign staff to facilitate the work of the working group.

TERMS OF REVIEW:

This document will be reviewed biannually by the SPDS Chair and AOAC staff.

DATES REVISED:

Stakeholder Panel

Voting Panel – A vetted, representative, and balanced subset of the assembled stakeholders. Ideally the number of voters represents $^1/_4$ to $^1/_3$ of the assembly.

Voting Guidelines – A. motions to create a consensus based standard (ex: voting on fitness for purpose statements or Standard Method Performance Requirements) require a 2/3 vote for the motion to carry.
B. Any other motion (ex: votes to clarify information for working groups, set priorities or direction, etc.) requires a majority vote to carry.

Expert Review Panel

Voting Panel – 7 – 10 vetted experts
Quorum - The presence of **7** members or **2/3** of total vetted ERP membership, whichever is greater.
Voting Guidelines – Motions to adopt a *First Action Official Method℠ of Analysis* carry by unanimous vote on first ballot. If not unanimous, negative votes must delineate scientific reasons, and can be overridden by 2/3 of voting ERP members after due consideration. Dissenting opinions are recorded.

Working Group

Voting Panel – There is no formal voting panel. Any interested and knowledgeable party may participate. Working groups sole purpose is to provide recommendations to stakeholder panels.

Voting Guidelines –majority vote carries all motions, dissenting opinions considered by assembly and recorded.

Helpful Definitions & Terminology

Quorum	The number of members who must be present in order to validly transact business. It is determined by the number of members present, not the number present and voting. (*Fundamentals of Parliamentary Law and Procedure, 3rd edition. p. 151*).
Representative Voting Panel Members	Every member has an obligation to vote and the right to abstain.
Abstentions	Abstentions reduce the number required to obtain a majority of those present and voting. They are only counted to confirm the presence of a quorum. (*Fundamentals of Parliamentary Law and Procedure, 3rd edition. p. 237).*
Order	Meetings should address only one item of business at one time (only one pending motion at a time). Chairs should not permit digression or introduction of different topics until the business at hand is resolved. No pending motions while changing topics. (*Fundamentals of Parliamentary Law and Procedure, 3rd edition. p. 1).* All business must be conducted with order and should be done fairly and impartially. The presiding officer should impartially ensure that each member has an opportunity to speak. *(Fundamentals of Parliamentary Law and Procedure, 3rd edition. pp. 1-2).*
Equality	All members have equal opportunity to propose motions, to participate in debate, to vote, to serve on committees or as an officer, to share in activities according to the member's abilities. *(Fundamentals of Parliamentary Law and Procedure, 3rd edition. p. 2).*
Justice	All members have the right to ask questions, to be informed, to have complex motions explained by the chair. *(Fundamentals of Parliamentary Law and Procedure, 3rd edition. p. 2).*
Minority Rights	Dissenting members have equal rights to voice opposing or minority opinions and strive to become the majority. *(Fundamentals of Parliamentary Law and Procedure, 3rd edition. p. 2).*
Majority Rights	No members, board, or officers have the right to dictate or control decisions unless the member grant such rights Members may not take any action in conflict with federal, regional or organizational laws or policies. Decisions are based on the will of the majority. *(Fundamentals of Parliamentary Law and Procedure, 3rd edition. p. 2).*

Appendix F: Guidelines for Standard Method Performance Requirements

Contents

Introduction to Standard Method Performance Requirements

Standard method performance requirements (SMPRs) are a unique and novel concept for the analytical methods community. SMPRs are voluntary consensus standards, developed by stakeholders, that prescribe the minimum analytical performance requirements for classes of analytical methods. In the past, analytical methods were evaluated and the results compared to a "gold standard" method, or if a gold standard method did not exist, then reviewers would decide retrospectively if the analytical performance was acceptable. Frequently, method developers concentrated on the process of evaluating the performance parameters of a method, and rarely set acceptance criteria. However, as the *Eurachem Guide* points out: " . . . the judgment of method suitability for its intended use is equally important . . ." (1) to the evaluation process.

International Voluntary Consensus Standards

An SMPR is a form of an international, voluntary consensus standard. A standard is an agreed, repeatable way of doing something that is published as document that contains a technical specification or other precise criteria designed to be used consistently as a rule, guideline, or definition. SMPRs are a *consensus* standards developed by stakeholders in a very controlled process that ensures that users, research organizations, government departments, and consumers work together to create a standard that meets the demands of the analytical community and technology. SMPRs are also *voluntary* standards. AOAC cannot, and does not, impose the use of SMPRs. Users are free to use SMPRs as they see fit. AOAC is very careful to include participants from as many regions of the world as possible so that SMPRs are accepted as *international* standards.

Guidance for Standard Method Performance Requirements

Commonly known as the "SMPR Guidelines." The first version of the SMPR Guidelines were drafted in 2010 in response to the increasing use and popularity of SMPRs as a vehicle to describe the analytical requirements of a method. Several early "acceptance criteria" documents were prepared for publication in late 2009, but the format of the acceptance criteria documents diverged significantly from one another in basic format. AOAC realized that a guidance document was needed to promote uniformity.

An early version of the SMPR Guidelines were used for a project to define the analytical requirements for endocrine disruptors in potable water. The guidelines proved to be extremely useful in guiding the work of the experts and resulted in uniform SMPRs. Subsequent versions of the SMPR Guidelines were used in the Stakeholder Panel for Infant Formula and Adult Nutritionals (SPIFAN) project with very positive results. The SMPR Guidelines are now published for the first time in the *Journal of AOAC INTERNATIONAL* and *Official Methods of Analysis*.

Users of the guidelines are advised that they are: (*1*) a *guidance* document, not a statute that users must conform to; and (*2*) a "living" document that is regularly updated, so users should check the AOAC website for the latest version before using these guidelines.

The SMPR Guidelines are intended to provide basic information for working groups assigned to prepare SMPRs. The guidelines consist of the standard format of an SMPR, followed by a series of informative tables and annexes.

SMPR Format

The general format for an SMPR is provided in *Annex A*.

Each SMPR is identified by a unique SMPR number consisting of the year followed by a sequential identification number (YYYY.XXX). An SMPR number is assigned when the standard is approved. By convention, the SMPR number indicates the year a standard is approved (as opposed to the year the standard is initiated). For example, SMPR 2010.003 indicates the third SMPR adopted in 2010.

The SMPR number is followed by a method name that must include the analyte(s), matrix(es), and analytical technique (unless the SMPR is truly intended to be independent of the analytical technology). The method name may also refer to a "common" name (e.g., "Kjeldahl" method).

The SMPR number and method name are followed by the name of the stakeholder panel or expert review panel that approved the SMPR, and the approval and effective dates.

Information about method requirements is itemized into nine categories: (*1*) intended use; (*2*) applicability; (*3*) analytical technique; (*4*) definitions; (*5*) method performance requirements; (*6*) system suitability; (*7*) reference materials; (*8*) validation guidance; and (*9*) maximum time-to-determination.

An SMPR for qualitative and/or identification methods may include up to three additional annexes: (*1*) inclusivity/selectivity panel; (*2*) exclusivity/cross-reactivity panel; and (*3*) environmental material panels. These annexes not required.

Informative tables.—The SMPR Guidelines contain seven informative tables that represent the distilled knowledge of many years of method evaluation, and are intended as guidance for SMPR working groups. The informative tables are not necessarily AOAC

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policy. SMPR working groups are expected to apply their expertise in the development of SMPRs.

Table A1: Performance Requirements. Provides recommended performance parameters to be included into an SMPR. Table A1 is organized by five method classifications: (*1*) main component quantitative methods; (*2*) trace or contaminant quantitative methods; (*3*) main component qualitative methods; (*4*) trace or contaminant quantitative methods; and (*5*) identification methods. The table is designed to accommodate both microbiological and chemical methods. Alternate microbiological/chemical terms are provided for equivalent concepts.

Table A2: Recommended Definitions. Provides definitions for standard terms in the SMPR Guidelines. AOAC relies on *The International Vocabulary of Metrology Basic and General Concepts and Associated Terms* (VIM) and the International Organization for Standadization (ISO) for definition of terms not included in Table A2.

Table A3: Recommendations for Evaluation. Provides general guidance for evaluation of performance parameters. More detailed evaluation guidance can be found in *Appendix D, Guidelines for Collaborative Study Procedures to Validate Characteristics of a Method of Analysis* (2); *Appendix I, Guidelines for Validation of Biological Threat Agent Methods and/or Procedures* (3); *Appendix K, AOAC Guidelines for Single-Laboratory Validation of Chemical Methods for Dietary Supplements and Botanicals* (4); Codex Alimentarius Codex Procedure Manual (5); and ISO Standard 5725-1-1994 (6).

Table A4: Expected Precision (Repeatability) as a Function of Analyte Concentration. The precision of a method is the closeness of agreement between independent test results obtained under stipulated conditions. Precision is usually expressed in terms of imprecision and computed as a relative standard deviation (RSD) of the test results. The imprecision of a method increases as the concentration of the analyte decreases. This table provides target RSDs for a range of analyte concentrations.

Table A5: Expected Recovery as a Function of Analyte Concentration. Recovery is defined as the ratio of the observed mean test result to the true value. The range of the acceptable mean recovery expands as the concentration of the analyte decreases. This table provides target mean recovery ranges for analyte concentrations from 1 ppb to 100%.

Table A6: Predicted Relative Standard Deviation of Reproducibility ($PRSD_R$). This table provides the calculated $PRSD_R$ using the Horwitz formula:

$$PRSD_R = 2C^{-0.15}$$

where C is expressed as a mass fraction.

Table A7: POD and Number of Test Portions. This table provides the calculated probability of detection (POD) for given sample sizes and events (detections). A method developer can use this table to determine the number of analyses required to obtain a specific POD.

Informative annexes.—The SMPR Guidelines contain informative annexes on the topics of classification of methods, POD model, HorRat values, reference materials, and method accuracy and review. As with the informative tables, these annexes are intended to provide guidance and information to the working groups.

Initiation of an SMPR

See Figure 1 for a schematic flowchart diagram of the SMPR development process.

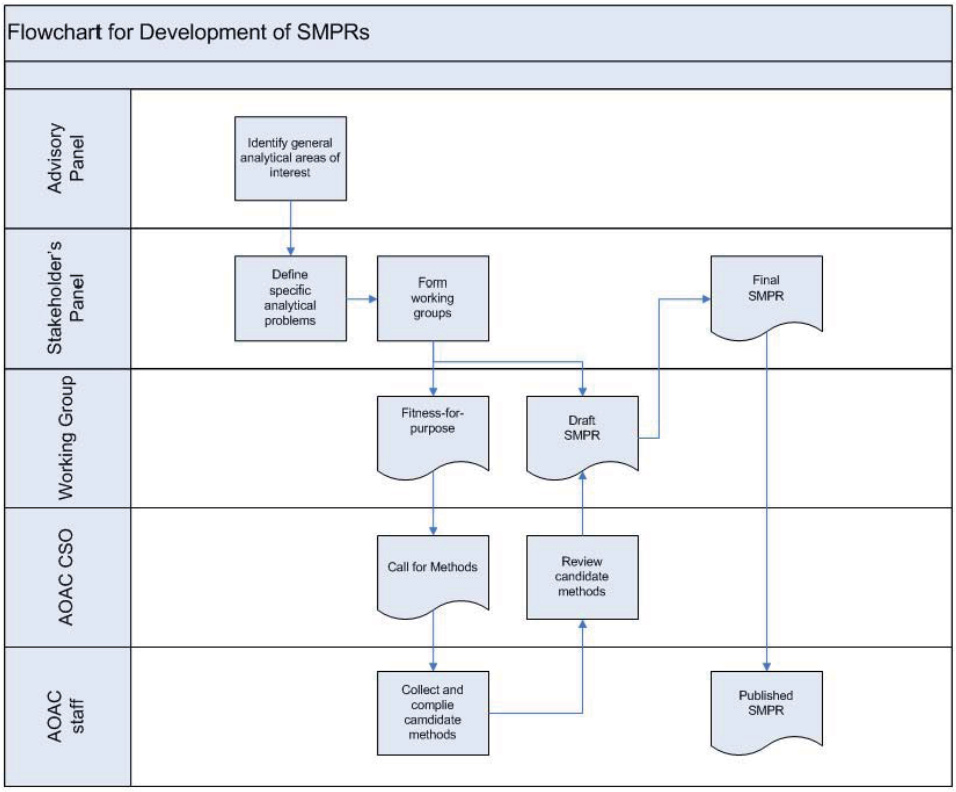

Figure 1. Schematic flowchart diagram of the SMPR development process.

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Advisory panels.—Most commonly, an SMPR is created in response to an analytical need identified by an advisory panel. Advisory panels normally consist of sponsors and key stakeholders who have organized to address analytical problems. Usually, the advisory panel identifies general analytical problems, such as the need to update analytical methods for determination of nutrients in infant formula. An advisory panel, with the input of appropriate subject matter experts, also prioritizes the specific analytical problems within the general topic. This panel is critical in planning for the stakeholder panel meeting.

Stakeholder panels.—After an advisory panel has identified a general analytical problem, AOAC announces the standards development activity, identifies stakeholders, and organizes a stakeholder panel. Membership on a stakeholder panel is open to anyone materially affected by the proposed standard. AOAC recruits scientists to participate on stakeholder panels on the basis of their expertise with the analytical problem identified by the advisory panel. Experts are recruited from academia, government, nongovernmental organizations (such as ISO), industry, contract research organizations, method developers, and instrument/equipment manufacturers. AOAC employs a representative voting panel model to ensure balance with regards to stakeholder perspective, and to ensure that no particular stakeholder perspective dominates the proceedings of the stakeholder panel. All stakeholder candidates are reviewed by the AOAC Chief Scientific Officer (CSO) for relevant qualifications, and again by the Official Methods Board to ensure that the stakeholder panel is balanced and all stakeholders are fairly represented.

Stakeholder panels are extremely important as they serve several functions: (*1*) identify specific analytical topics within the general analytical problem described by the advisory panel; (*2*) form working groups to address the specific analytical topics; (*3*) identify additional subject matter experts needed for the working groups; (*4*) provide oversight of the SMPR development; and (*5*) formally adopt SMPRs originally drafted by working groups.

Working groups.—Working groups are formed by the stakeholder panel when a specific analytical topic has been identified. The primary purpose of a working group is to draft an SMPR. Working groups may also be formed to make general recommendations, such as developing a common definition to be used by multiple working groups. For example, SPIFAN formed a working group to create a definition for "infant formula" that could be shared and used by all of the SPIFAN working groups.

The process of drafting an SMPR usually requires several months, and several meetings and conference calls. An SMPR drafted by a working group is presented to a stakeholder panel. A stakeholder panel may revise, amend, or adopt a proposed SMPR on behalf of AOAC.

Fitness-for-Purpose Statement and Call for Methods

One of the first steps in organizing a project is creating a fitness-for-purpose statement. In AOAC, the fitness-for-purpose statement is a very general description of the methods needed. It is the responsibility of a working group chair to draft a fitness-for-purpose statement. A working group chair is also asked to prepare a presentation with background information about the analyte, matrix, and the nature of the analytical problem. A working group chair presents the background information and proposes a draft fitness-for-purpose statement to the presiding stakeholder panel. The stakeholder panel is asked to endorse the fitness-for-purpose statement.

The AOAC CSO prepares a call for methods based on the stakeholder panel-approved fitness-for-purpose statement. The call for methods is posted on the AOAC website and/or e-mailed to the AOAC membership and other known interested parties. AOAC staff collects and compiles candidate methods submitted in response to the call for methods. The CSO reviews and categorizes the methods.

Creating an SMPR

Starting the process of developing an SMPR can be a daunting challenge. In fact, drafting an SMPR should be a daunting challenge because the advisory panel has specifically identified an analytical problem that has yet to be resolved. Completing an SMPR can be a very rewarding experience because working group members will have worked with their colleagues through a tangle of problems and reached a consensus where before there were only questions.

It is advisable to have some representative candidate methods available for reference when a working group starts to develop an SMPR. These methods may have been submitted in response to the call for methods, or may be known to a working group member. In any case, whatever the origin of the method, candidate methods may assist working group members to determine reasonable performance requirements to be specified in the SMPR. The performance capabilities of exisiting analytical methodologies is a common question facing a working group.

Normally, a working chair and/or the AOAC CSO prepares a draft SMPR. A draft SMPR greatly facilitates the process and provides the working group with a structure from which to work.

Working group members are advised to first consider the "intended use" and "maximum time-to-determination" sections as this will greatly affect expectations for candidate methods. For example, methods intended to be used for surveillance probably need to be quick but do not require a great deal of precision, and false-positive results might be more tolerable. Whereas methods intended to be used for dispute resolution will require better accuracy, precision, and reproducibility, but time to determination is not as important.

Once a working group has agreed on the intended use of candidate methods, then it can begin to define the applicability of candidate methods. The applicability section of the SMPR is one of the most important, and sometimes most difficult, sections of the SMPR. The analyte(s) and matrixes must be explicitly identified. For chemical analytes, International Union of Pure and Applied Chemistry (IUPAC) nomenclature and/or Chemical Abstracts Service (CAS) registry numbers should be specified. Matrixes should be clearly identified including the form of the matrix such as raw, cooked, tablets, powders, etc. The nature of the matrix may affect the specific analyte. It may be advantageous to fully identify and describe the matrix before determining the specific analyte(s). It is not uncommon for working groups to revise the initial definition of the analyte(s) after the matrix(es) has been better defined.

Table 1. Example of method performance table for a single analyte

Analytical range	7.0–382.6 µg/mL	
Limit of quantitation (LOQ)	≤7.0 µg/mL	
Repeatability (RSD_r)	<10 µg/mL	≤8%
	≥10 µg/mL	≤6%

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Table 2. Example of method performance table for multiple analytes

	Analyte 1		Analyte 2		Analyte 3	
Analytical range	10–20 µg/mL		100–200 µg/mL		200–500 µg/mL	
Limit of quantitation (LOQ)	≤10 µg/mL		≤100 µg/mL		≤200 µg/mL	
Repeatability (RSD_r)	<10 µg/mL	≤8%	<10 µg/mL	≤8%	<200 µg/mL	≤10%
	≥10 µg/mL	≤6%	≥10 µg/mL	≤6%	≥200 µg/mL	≤8%

For projects with multiple analytes, for example, vitamins A, D, E, and K in infant formula, it may be useful to organize a separate working group to fully describe the matrix(es) so that a common description of the matrix(es) can be applied to all of the analytes.

For single analyte SMPRs, it is most common to organize the method performance requirements into a table with 2–3 columns as illustrated in Table 1. For multiple analyte SMPRs, it is often convenient to present the requirements in an expanded table with analytes forming additional columns as illustrated in Table 2.

Once the intended use, analytical techniques, and method performance requirements have been determined, then a working group can proceed to consider the quality control parameters, such as the minimum validation requirements, system suitability procedures, and reference materials (if available). It is not uncommon that an appropriate reference material is not available. *Annex F* of the SMPR Guidelines provides comprehensive guidance for the development and use of in-house reference materials.

Most working groups are able to prepare a consensus SMPR in about 3 months.

Open Comment Period

Once a working group has produced a draft standard, AOAC opens a comment period for the standard. The comment period provides an opportunity for other stakeholders to state their perspective on the draft SMPR. All collected comments are reviewed by the AOAC CSO and the working group chair, and the comments are reconciled. If there are significant changes required to the draft standard as a result of the comments, the working group is convened to discuss and any unresolved issues will be presented for discussion at the stakeholder panel meeting.

Submission of Draft SMPRs to the Stakeholder Panel

Stakeholder panels meet several times a year at various locations. The working group chair (or designee) presents a draft SMPR to the stakeholder panel for review and discussion. A working group chair is expected to be able to explain the conclusions of the working group, discuss comments received, and to answer questions from the stakeholder panel. The members of the stakeholder panel may revise, amend, approve, or defer a decision on the proposed SMPR. A super majority of 2/3 or more of those voting is required to adopt an SMPR as an AOAC voluntary consensus standard.

Publication

Adopted SMPRs are prepared for publication by AOAC staff, and are published in the *Journal of AOAC INTERNATIONAL* and in the AOAC *Official Methods of Analysis*℠ compendium. Often, the AOAC CSO and working group chair prepare a companion article to introduce an SMPR and describe the analytical issues considered and resolved by the SMPR. An SMPR is usually published within 6 months of adoption.

Conclusion

SMPRs are a unique and novel concept for the analytical methods community. SMPRs are voluntary, consensus standards developed by stakeholders that prescribe the minimum analytical performance requirements for classes of analytical methods. The SMPR Guidelines provide a structure for working groups to use as they develop an SMPR. The guidelines have been employed in several AOAC projects and have been proven to be very useful. The guidelines are not a statute that users must conform to; they are a "living" document that is regularly updated, so users should check the AOAC website for the latest version before using the guidelines.

References

(1) Eurachem, *The Fitness for Purpose of Analytical Methods: A Laboratory Guide to Method Validation and Related Topics, Validation*, http://www.eurachem.org/guides/pdf/valid.pdf, posted December 1998, accessed March 2012

(2) *Guidelines for Collaborative Study Procedures to Validate Characteristics of a Method of Analysis* (2012) *Official Methods of Analysis, Appendix D*, AOAC INTERNATIONAL, Gaithersburg, MD

(3) *AOAC INTERNATIONAL Methods Committee Guidelines for Validation of Biological Threat Agent Methods and/or Procedures* (2012) *Official Methods of Analysis,* 19th Ed., *Appendix I, Calculation of CPOD and dCPOD Values from Qualitative Method Collaborative Study Data*, AOAC INTERNATIONAL, Gaithersburg, MD

(4) *AOAC Guidelines for Single-Laboratory Validation of Chemical Methods for Dietary Supplements and Botanicals* (2012) *Official Methods of Analysis*, 19th Ed., *Appendix K*, AOAC INTERNATIONAL, Gaithersburg, MD

(5) Codex Alimentarius Codex Procedure Manual

(6) International Organization for Standardization, Geneva, Switzlerland

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ANNEX A
Format of a
Standard Method Performance Requirement

AOAC SMPR YYYY.XXX
(YYYY = Year; XXX = sequential identification number)

Method Name: Must include the analyte(s), matrix(es), and analytical technique [unless the standard method performance requirement (SMPR) is truly intended to be independent of the analytical technology]. The method name may refer to a "common" name (e.g., "Kjeldahl" method).

Approved By: Name of stakeholder panel or expert review panel

Final Version Date: Date

Effective Date: Date

1. Intended Use: Additional information about the method and conditions for use.

2. Applicability: List matrixes if more than one. Provide details on matrix such as specific species for biological analytes, or International Union of Pure and Applied Chemistry (IUPAC) nomenclature and Chemical Abstracts Service (CAS) registry number for chemical analytes. Specify the form of the matrix such as raw, cooked, tablets, powders, etc.

3. Analytical Technique: Provide a detailed description of the analytical technique if the SMPR is to apply to a specific analytical technique; or state that the SMPR applies to any method that meets the method performance requirements.

4. Definitions: List and define terms used in the performance parameter table (*see* Table A2 for list of standard terms).

5. Method Performance Requirements: List the performance parameters and acceptance criteria appropriate for each method/analyte/matrix. *See* Table A1 for appropriate performance requirements.

If more than one analyte/matrix, and if acceptance criteria differ for analyte/matrix combinations then organize a table listing each analyte/matrix combination and its minimum acceptance criteria for each performance criteria.

6. System Suitability Tests and/or Analytical Quality Control: Describe minimum system controls and QC procedures.

7. Reference Material(s): Identify the appropriate reference materials if they exist, or state that reference materials are not available. Refer to *Annex E* (*AOAC Method Accuracy Review*) for instructions on the use of reference materials in evaluations.

8. Validation Guidance: Recommendations for type of evaluation or validation program such as single-laboratory validation (SLV), *Official Methods of Analysis*℠ (OMA), or *Performance Tested Methods*℠ (PTM).

9. Maximum Time-to-Determination: Maximum allowable time to complete an analysis starting from the test portion preparation to final determination or measurement.

Annex I: Inclusivity/Selectivity Panel. Recommended for qualitative and identification method SMPRs.

Annex II: Exclusivity/Cross-Reactivity Panel. Recommended for qualitative and identification method SMPRs.

Annex III: Environmental Materials Panel. Recommended for qualitative and identification method SMPRs.

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Table A1. Performance requirements

Classifications of methods[a]				
Quantitative method		Qualitative method		
Main component[b]	Trace or contaminant[c]	Main component[b]	Trace or contaminant[c]	Identification method
Parameter				
Single-laboratory validation				
Applicable range	Applicable range	Inclusivity/selectivity	Inclusivity/selectivity	Inclusivity/selectivity
Bias[d]	Bias[d]	Exclusivity/cross-reactivity	Exclusivity/cross-reactivity	Exclusivity/cross-reactivity
Precision	Precision	Environmental interference	Environmental interference	Environmental interference
Recovery	Recovery	Laboratory variance	Laboratory variance	
Limit of quantitation (LOQ)	LOQ			
		Probability of detection (POD)[e]	POD at AMDL[f]	Probability of identification (POI)
Reproducibility				
RSD_R or target measurement uncertainty	RSD_R or target measurement uncertainty	POD (0)	POD (0)	POI (c)
		POD (c)	POD (c)	
		Laboratory POD[g]	Laboratory POD[g]	Laboratory POI

[a] *See Annex B* for additional information on classification of methods.

[b] ≥100 g/kg.

[c] <100 g/kg.

[d] If a reference material is available.

[e] At a critical level.

[f] AMDL = Acceptable minimum detection level.

[g] LPOD = CPOD.

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Table A2. Recommended definitions

Bias	Difference between the expectation of the test results and an accepted reference value. Bias is the total systematic error as contrasted to random error. There may be one or more systematic error components contributing to the bias.
Environmental interference	Ability of the assay to detect target organism in the presence of environmental substances and to be free of cross reaction from environmental substances.
Exclusivity	Strains or isolates or variants of the target agent(s) that the method must not detect.
Inclusivity	Strains or isolates or variants of the target agent(s) that the method can detect.
Laboratory probability of detection (POD)	Overall fractional response (mean POD = CPOD) for the method calculated from the pooled POD_j responses of the individual laboratories (j = 1, 2, ..., L).[a] *See Annex C*.
Limit of quantitation (LOQ)	Minimum concentration or mass of analyte in a given matrix that can be reported as a quantitative result.
POD (0)	Probability of the method giving a (+) response when the sample is truly without analyte.
POD (c)	Probability of the method giving a (–) response when the sample is truly without analyte.
POD	Proportion of positive analytical outcomes for a qualitative method for a given matrix at a given analyte level or concentration. Consult *Annex C* for a full explanation.
Probability of identification (POI)	Expected or observed fraction of test portions at a given concentration that gives positive result when tested at a given concentration. Consult *Probability of Identification (POI): A Statistical Model for the Validation of Qualitative Botanical Identification Methods*.[c]
Precision (repeatability)	Closeness of agreement between independent test results obtained under stipulated conditions. The measure of precision is usually expressed in terms of imprecision and computed as a standard deviation of the test results.[d]
Recovery	Fraction or percentage of the analyte that is recovered when the test sample is analyzed using the entire method. There are two types of recovery: (*1*) Total recovery based on recovery of the native plus added analyte, and (*2*) marginal recovery based only on the added analyte (the native analyte is subtracted from both the numerator and denominator).[e]
Repeatability	Precision under repeatability conditions.
Repeatability conditions	Conditions where independent test results are obtained with the same method on identical test items in the same laboratory by the same operator using the same equipment within short intervals of time.
Reproducibility	Precision under reproducibility conditions.
Reproducibility conditions	Conditions where independent test results are obtained with the same method on identical test items in different laboratories with different operators using different equipment.
Relative standard deviation (RSD)	$RSD = s_i \times 100/\bar{x}$
Standard deviation (s_i)	$s_i = [\Sigma(x_i - \bar{x})^2/n]^{0.5}$

[a] *AOAC INTERNATIONAL Methods Committee Guidelines for Validation of Biological Threat Agent Methods and/or Procedures* (*Calculation of CPOD and dCPOD Values from Qualitative Method Collaborative Study Data*), *J. AOAC Int*. **94**, 1359(2011) and *Official Methods of Analysis of AOAC INTERNATIONAL* (2012) 19th Ed., *Appendix I*.

[b] *International Vocabulary of Metrology (VIM)—Basic and General Concepts and Associated Terms* (2008) JCGM 200:2008, Joint Committee for Guides in Metrology (JCGM), www.bipm.org

[c] LaBudde, R.A., & Harnly, J.M. (2012) *J. AOAC Int*. **95**, 273–285.

[d] ISO 5725-1-1994.

[e] *Official Methods of Analysis* (2012) *Appendix D* (*Guidelines for Collaborative Study Procedures to Validate Characteristics of a Method of Analysis*), AOAC INTERNATIONAL, Gaithersburg, MD.

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Table A3. Recommendations for evaluation

Bias (if a reference material is available)	A minimum of five replicate analyses of a Certified Reference Material.[a]
Environmental interference	Analyze test portions containing a specified concentration of one environmental materials panel member. Materials may be pooled. Consult with AOAC statistician.
Exclusivity/cross-reactivity	Analyze one test portion containing a specified concentration of one exclusivity panel member. More replicates can be used. Consult with AOAC statistician.
Inclusivity/selectivity	Analyze one test portion containing a specified concentration of one inclusivity panel member. More replicates can be used. Consult with AOAC statistician.
Limit of quantitation (LOQ)	Estimate the LOQ = average (blank) + 10 × s_0 (blank). Measure blank samples with analyte at the estimated LOQ. Calculate the mean average and standard deviation of the results. Guidance[b]: For ML ≥ 100 ppm (0.1 mg/kg): LOD = ML × 1/5. For ML < 100 ppm (0.1 mg/kg): LOD = ML × 2/5.
Measurement uncertainty	Use ISO 21748: *Guidance for the use of repeatability, reproducibility, and trueness estimates in measurement uncertainty estimation to analyze data collected for bias, repeatability, and intermediate precision to estimate measurement uncertainty*.
POD(0)	Use data from collaborative study.
POD (c)	
Repeatability	Prepare and homogenize three unknown samples at different concentrations to represent the full, claimed range of the method. Analyze each unknown sample by the candidate method seven times, beginning each analysis from weighing out the test portion through to final result with no additional replication (unless stated to do so in the method). All of the analyses for one unknown sample should be performed within as short a period of time as is allowed by the method. The second and third unknowns may be analyzed in another short time period. Repeat for each claimed matrix.
Probability of detection (POD)	Determine the desired POD at a critical concentration. Consult with Table A7 to determine the number of test portions required to demonstrate the desired POD.
Probability of identification (POI)	Consult *Probability of Identification (POI): A Statistical Model for the Validation of Qualitative Botanical Identification Methods*[c].
Recovery	Determined from spiked blanks or samples with at least seven independent analyses per concentration level at a minimum of three concentration levels covering the analytical range. Independent means at least at different times. If no confirmed (natural) blank is available, the average inherent (naturally containing) level of the analyte should be determined on at least seven independent replicates. Marginal % recovery = $(C_f - C_u) \times 100/C_A$ Total % recovery = $100(C_f)/(C_u + C_A)$ where C_f = concentration of fortified samples, C_u = concentration of unfortified samples, and C_A = concentration of analyte added to the test sample.[d] Usually total recovery is used unless the native analyte is present in amounts greater than about 10% of the amount added, in which case use the method of addition.[e]
Reproducibility (collaborative or interlaboratory study)	Quantitative methods: Recruit 10–12 collaborators; must have eight valid data sets; two blind duplicate replicates at five concentrations for each analyte/matrix combination to each collaborator.
	Qualitative methods: Recruit 12–15 collaborators; must have 10 valid data sets; six replicates at five concentrations for each analyte/matrix combination to each collaborator.

[a] *Guidance for Industry for Bioanalytical Method Validation* (May 2001) U.S. Department of Health and Human Services, U.S. Food and Drug Administration, Center for Drug Evaluation and Research (CDER), Center for Veterinary Medicine (CVM).

[b] Codex Alimentarius Codex Procedure Manual.

[c] LaBudde, R.A., & Harnly, J.M. (2012) *J. AOAC Int.* **95**, 273–285.

[d] *Guidelines for Collaborative Study Procedures to Validate Characteristics of a Method of Analysis* (2012) *Official Methods of Analysis*, 19th Ed., *Appendix D,* AOAC INTERNATIONAL, Gaithersburg, MD.

[e] *AOAC Guidelines for Single-Laboratory Validation of Chemical Methods for Dietary Supplements and Botanicals* (2012) *Official Methods of Analysis*, 19th Ed., *Appendix K*, AOAC INTERNATIONAL, Gaithersburg, MD.

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Table A4. Expected precision (repeatability) as a function of analyte concentration[a]

Analyte, %	Analyte ratio	Unit	RSD, %
100	1	100%	1.3
10	10^{-1}	10%	1.9
1	10^{-2}	1%	2.7
0.01	10^{-3}	0.1%	3.7
0.001	10^{-4}	100 ppm (mg/kg)	5.3
0.0001	10^{-5}	10 ppm (mg/kg)	7.3
0.00001	10^{-6}	1 ppm (mg/kg)	11
0.000001	10^{-7}	100 ppb (µg/kg)	15
0.0000001	10^{-8}	10 ppb (µg/kg)	21
0.00000001	10^{-9}	1 ppb (µg/kg)	30

[a] Table excerpted from *AOAC Peer-Verified Methods Program, Manual on Policies and Procedures* (1998) AOAC INTERNATIONAL, Gaithersburg, MD.

The precision of a method is the closeness of agreement between independent test results obtained under stipulated conditions. Precision is usually expressed in terms of imprecision and computed as a relative standard deviation of the test results. The imprecision of a method increases as the concentration of the analyte decreases. This table provides targets RSDs for a range of analyte concentrations.

Table A5. Expected recovery as a function of analyte concentration[a]

Analyte, %	Analyte ratio	Unit	Mean recovery, %
100	1	100%	98–102
10	10^{-1}	10%	98–102
1	10^{-2}	1%	97–103
0.01	10^{-3}	0.1%	95–105
0.001	10^{-4}	100 ppm	90–107
0.0001	10^{-5}	10 ppm	80–110
0.00001	10^{-6}	1 ppm	80–110
0.000001	10^{-7}	100 ppb	80–110
0.0000001	10^{-8}	10 ppb	60–115
0.00000001	10^{-9}	1 ppb	40–120

[a] Table excerpted from *AOAC Peer-Verified Methods Program, Manual on Policies and Procedures* (1998) AOAC INTERNATIONAL, Gaithersburg, MD.

Recovery is defined as the ratio of the observed mean test result to the true value. The range of the acceptable mean recovery expands as the concentration of the analyte decreases. This table provides target mean recovery ranges for analyte concentrations from 100% to 1 ppb.

Table A6. Predicted relative standard deviation of reproducibility ($PRSD_R$)[a]

Concentration (C)	Mass fraction (C)	$PRSD_R$, %
100%	1.0	2
1%	0.01	4
0.01%	0.0001	8
1 ppm	0.000001	16
10 ppb	0.00000001	32
1 ppb	0.000000001	45

[a] Table excerpted from *Definitions and Calculations of HorRat Values from Intralaboratory Data*, HorRat for SLV.doc, 2004-01-18, AOAC INTERNATIONAL, Gaithersburg, MD.

Predicted relative standard deviation = $PRSD_R$. Reproducibility relative standard deviation calculated from the Horwitz formula:

$$PRSD_R = 2C^{-0.15}, \text{ where C is expressed as a mass fraction}$$

This table provides the calculated $PRSD_R$ for a range of concentrations. *See Annex D* for additional information.

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Table A7. POD and number of test portions[a,b]

	Sample size required for proportion						
Assume	1. Binary outcome (occur/not occur). 2. Constant probability rho of event occurring. 3. Independent trials (e.g., simple random sample). 4. Fixed number of trials (*N*)						
Inference	95% Confidence interval lies entirely at or above specified minimum rho						
Desired	Sample size *N* needed						
Minimum probability rho, %	Sample size (*N*)	Minimum No. events (*x*)	Maximum No. nonevents (*y*)	1-Sided lower confidence limit on rho[c], %	Expected lower confidence limit on rho, %	Expected upper confidence limit on rho, %	Effective AOQL[d] rho, %
50	3	3	0	52.6	43.8	100.0	71.9
50	10	8	2	54.1	49.0	94.3	71.7
50	20	14	6	51.6	48.1	85.5	66.8
50	40	26	14	52.0	49.5	77.9	63.7
50	80	48	32	50.8	49.0	70.0	59.5
55	4	4	0	59.7	51.0	100.0	75.5
55	10	9	1	65.2	59.6	100.0	79.8
55	20	15	5	56.8	53.1	88.8	71.0
55	40	28	12	57.1	54.6	81.9	68.2
55	80	52	28	55.9	54.1	74.5	64.3
60	5	5	0	64.9	56.5	100.0	78.3
60	10	9	1	65.2	59.6	100.0	79.8
60	20	16	4	62.2	58.4	91.9	75.2
60	40	30	10	62.4	59.8	85.8	72.8
60	80	56	24	61.0	59.2	78.9	69.1
65	6	6	0	68.9	61.0	100.0	80.5
65	10	9	1	65.2	59.6	100.0	79.8
65	20	17	3	67.8	64.0	94.8	79.4
65	40	31	9	65.1	62.5	87.7	75.1
65	80	59	21	65.0	63.2	82.1	72.7
70	7	7	0	72.1	64.6	100.0	82.3
70	10	10	0	78.7	72.2	100.0	86.1
70	20	18	2	73.8	69.9	97.2	83.6
70	40	33	7	70.7	68.0	91.3	79.7
70	80	63	17	70.4	68.6	86.3	77.4
75	9	9	0	76.9	70.1	100.0	85.0
75	10	10	0	78.7	72.2	100.0	86.1
75	20	19	1	80.4	76.4	100.0	88.2
75	40	35	5	76.5	73.9	94.5	84.2
75	80	67	13	75.9	74.2	90.3	82.2
80	11	11	0	80.3	74.1	100.0	87.1
80	20	19	1	80.4	76.4	100.0	88.2
80	40	37	3	82.7	80.1	97.4	88.8
80	80	70	10	80.2	78.5	93.1	85.8
85	20	20	0	88.1	83.9	100.0	91.9
85	40	38	2	86.0	83.5	98.6	91.1
85	80	74	6	86.1	84.6	96.5	90.6
90	40	40	0	93.7	91.2	100.0	95.6
90	60	58	2	90.4	88.6	99.1	93.9
90	80	77	3	91.0	89.5	98.7	94.1
95	60	60	0	95.7	94.0	100.0	97.0
95	80	80	0	96.7	95.4	100.0	97.7
95	90	89	1	95.2	94.0	100.0	97.0
95	96	95	1	95.5	94.3	100.0	97.2
98	130	130	0	98.0	97.1	100.0	98.6
98	240	239	1	98.2	97.7	100.0	98.8
99	280	280	0	99.0	98.6	100.0	99.3
99	480	479	1	99.1	98.8	100.0	99.4

[a] Table excerpted from Technical Report TR308, *Sampling plans to verify the proportion of an event exceeds or falls below a specified value*, LaBudde, R. (June 4, 2010) (not published). The table was produced as part of an informative report for the Working Group for Validation of Identity Methods for Botanical Raw Materials commissioned by the AOAC INTERNATIONAL Presidential Task Force on Dietary Supplements. The project was funded by the Office of Dietary Supplements, National Institutes of Health.

[b] Copyright 2010 by Least Cost Formulations, Ltd. All rights reserved.

[c] Based on modified Wilson score 1-sided confidence interval.

[d] AOQL = Average outgoing quality level.

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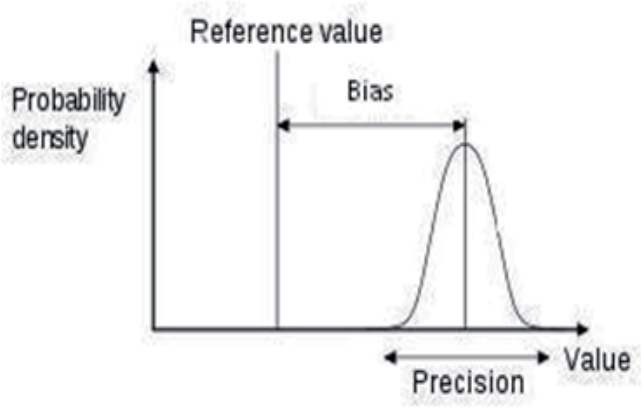

Figure A1. Relationship between precision versus bias (trueness). Trueness is reported as bias. Bias is defined as the difference between the test results and an accepted reference value.

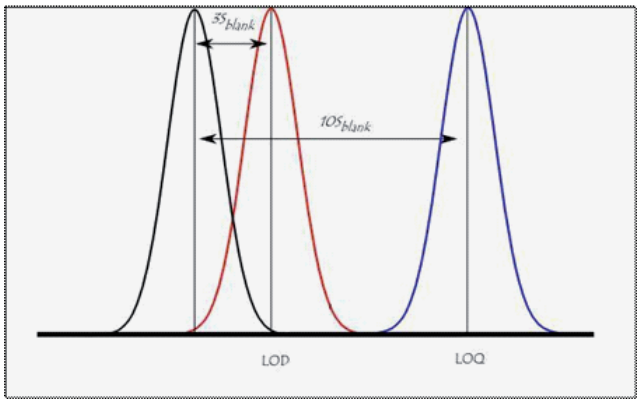

Figure A2. Relationship between LOD and LOQ. LOD is defined as the lowest quantity of a substance that can be distinguished from the absence of that substance (a blank value) within a stated confidence limit. LOQ is the level above which quantitative results may be obtained with a stated degree of confidence.

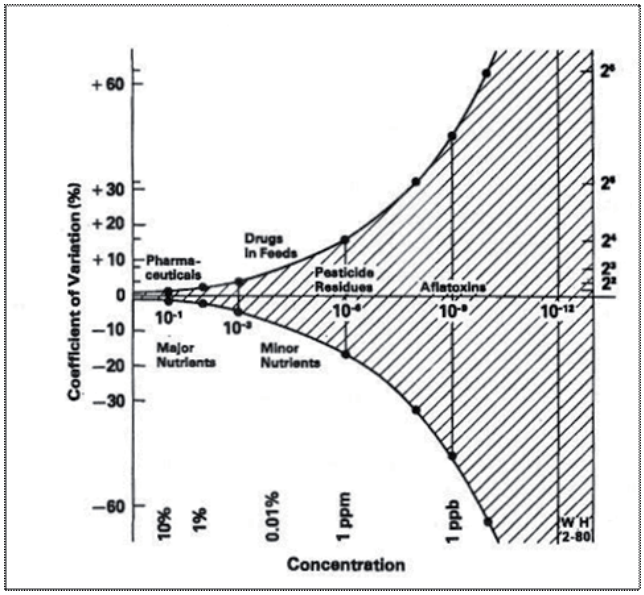

Figure A3. Horwitz Curve, illustrating the exponential increase in the coefficient of variation as the concentration of the analyte decreases [*J. AOAC Int*. 89, 1095(2006)].

ANNEX B
Classification of Methods

The following guidance may be used to determine which performance parameters in Table A1 apply to different classifications of methods. AOAC INTERNATIONAL does not recognize the term "semiquantitative" as a method classification. Methods that have been self-identified as semiquantitative will be classified into one of the following five types:

Type I: Quantitative Methods

Characteristics: Generates a continuous number as a result.

Recommendation: Use performance requirements specified for quantitative method (main or trace component). Use recovery range and maximum precision variation in Tables A4 and A5.

In some cases and for some purposes, methods with less accuracy and precision than recommended in Tables A4 and A5 may be acceptable. Method developers should consult with the appropriate method committee to determine if the recommendations in Tables A4 and A5 do or do not apply to their method.

Type II: Methods that Report Ranges

Characteristics: Generates a "range" indicator such as 0, low, moderate, and high.

Recommendation: Use performance requirements specified for qualitative methods (main component). Specify a range of POD for each range "range" indicator.

Type III: Methods with Cutoff Values

Characteristics: Method may generate a continuous number as an interim result (such as a CT value for a PCR method), which is not reported but converted to a qualitative result (presence/ absence) with the use of a cutoff value.

Recommendation: Use performance requirements specified for qualitative methods.

Type IV: Qualitative Methods

Characteristics: Method of analysis whose response is either the presence or absence of the analyte detected either directly or indirectly in a specified test portion.

Recommendation: Use performance requirements specified for qualitative methods.

Type V: Identification Methods

Characteristics: Method of analysis whose purpose is to determine the identity of an analyte.

Recommendation: Use performance requirements specified for identification methods.

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ANNEX C
Understanding the POD Model

Excerpted from AOAC INTERNATIONAL Methods Committee Guidelines for Validation of Biological Threat Agent Methods and/or Procedures, J. AOAC Int. ***94****, 1359(2011) and Official Methods of Analysis of AOAC INTERNATIONAL (2012) 19th Ed., Appendix I.*

The Probability of Detection (POD) model is a way of characterizing the performance of a qualitative (binary) method. A binary qualitative method is one that gives a result as one of two possible outcomes, either positive or negative, presence/absence, or +/–.

The single parameter of interest is the POD, which is defined as the probability at a given concentration of obtaining a positive response by the detection method. POD is assumed to be dependent on concentration, and generally, the probability of a positive response will increase as concentration increases.

For example, at very low concentration, the expectation is that the method will not be sensitive to the analyte, and at very high concentration, a high probability of obtaining a positive response is desired. The goal of method validation is to characterize how method response transitions from low concentration/low response to high concentration/high response.

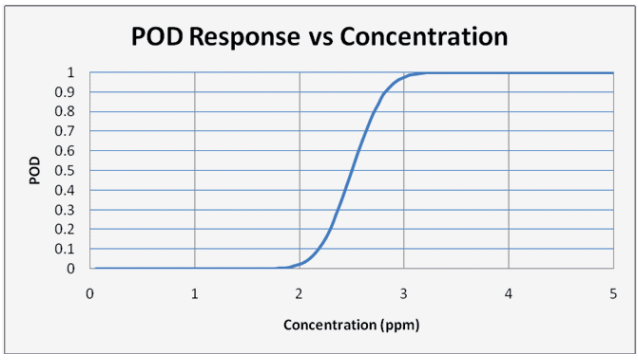

Figure C1. Theoretical POD curve for a qualitative detection method.

POD is always considered to be dependent upon analyte concentration. The POD curve is a graphical representation of method performance, where the probability is plotted as a function of concentration (*see*, for example, Figure C1).

The POD model is designed to allow an objective description of method response without consideration to an a priori expectation of the probabilities at given concentrations. The model is general enough to allow comparisons to any theoretical probability function.

The POD model is also designed to allow for an independent description of method response without consideration to the response of a reference method. The model is general enough to allow for comparisons between reference and candidate method responses, if desired.

Older validation models have used the terms "sensitivity," "specificity," "false positive," and "false negative" to describe method performance. The POD model incorporates all of the performance concepts of these systems into a single parameter, POD.

For example, false positive has been defined by some models as the probability of a positive response, given the sample is truly negative (concentration = 0). The equivalent point on the POD curve for this performance characteristic is the value of the curve at Conc = 0.

Similarly, false negative has sometimes been defined as the probability of a negative response when the sample is truly positive (concentration >0). In the POD curve, this would always be specific to a given sample concentration, but would be represented as the distance from the POD curve to the POD = 1 horizontal top axis at all concentrations except C = 0.

The POD model incorporates all these method characteristics into a single parameter, which is always assumed to vary by concentration. In other models, the terms "false positive," "false negative," "sensitivity," and "specificity" have been defined in a variety of ways, usually not conditional on concentration. For these reasons, these terms are obsolete under this model (*see* Table C1).

The terms "sensitivity," "specificity," "false positive," and "false negative" are obsolete under the POD model (*see* Figure C2).

Table C1. Terminology

Traditional terminology	Concept	POD equivalent	Comment
False positive	Probability of the method giving a (+) response when the sample is truly without analyte	POD(0) POD at conc = 0	POD curve value at conc = 0; "*Y*-intercept" of the POD curve
Specificity	Probability of the method giving a (-) response when the sample is truly without analyte	1-POD(0)	Distance along the POD axis from POD = 1 to the POD curve value
False negative (at a given concentration)	Probability of a (–) response at a given concentration	1-POD(c)	Distance from the POD curve to the POD = 1 "top axis" in the vertical direction
Sensitivity (at a given concentration)	Probability of a (+) response at a given concentration	POD(c)	Value of the POD curve at any given concentration
True negative	A sample that contains no analyte	C = 0	Point on concentration axis where c = 0
True positive	A sample that contains analyte at some positive concentration	C > 0	Range of concentration where c > 0

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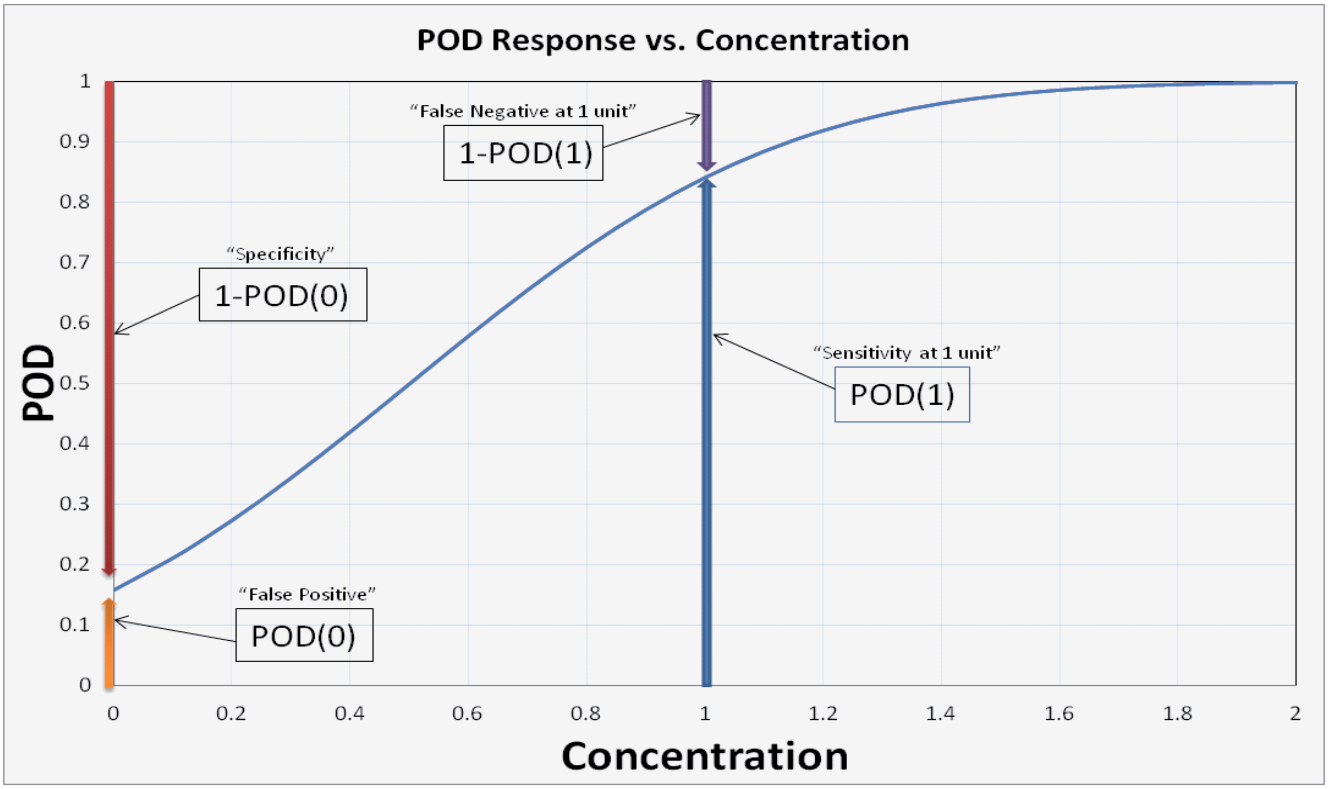

Figure C2. Comparison of POD model terminology to other obsolete terms.

ANNEX D
Definitions and Calculations of HorRat Values from Intralaboratory Data

Excerpted from Definitions and Calculations of HorRat Values from Intralaboratory Data, AOAC INTERNATIONAL, HorRat for SLV.doc, 2004-01-18.

1. Definitions

1.1 Replicate Data

Data developed under common conditions in the same laboratory: simultaneous performance, or, if necessary to obtain sufficient values, same series, same analyst, same day. Such data provides "repeatability statistical parameters."

1.2 Pooled Data

Replicate data developed in the same laboratory under different conditions but considered sufficiently similar that, for the purpose of statistical analysis, they may be considered together. These may include different runs, different instruments, different analysts, and different days.

1.3 Average

0 = Sum of the individual values, x_i, divided by the number of individual values, *n*.

$$0 = (\Sigma\, x_i)/n$$

1.4 Standard Deviation

$$s_i = [\Sigma(x_i - (\bar{x})^2/n]^{0.5}$$

1.5 Relative Standard Deviation

$$RSD = s_i \times 100/\bar{x}$$

1.5.1 Repeatability Relative Standard Deviation [RSD(r) or RSD_r]

The relative standard deviation calculated from within-laboratory data.

1.5.2 Reproducibility Relative Standard Deviation [RSD(R) or RSD_R]

The relative standard deviation calculated from among-laboratory data.

Table D1. Predicted relative standard deviations

Concentration (C)	Mass fraction (C)	$PRSD_R$, %
100%	1.0	2
1%	0.01	4
0.01%	0.0001	8
1 ppm	0.000001	16
10 ppb	0.00000001	32
1 ppb	0.000000001	45

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1.6 Mass Fraction

Concentration, C, expressed as a decimal fraction. For calculating and reporting statistical parameters, data may be expressed in any convenient units (e.g., %, ppm, ppb, mg/g, µg/g; µg/kg; µg/L, µg/µL, etc.). For reporting HorRat values, data must be reported as a mass fraction where the units of the numerator and denominator are the same: e.g., for 100% (pure materials), the mass fraction C = 1.00; for 1 µg/g (ppm), C = 0.000001 = (E-6). *See* Table D1 for other examples.

1.7 Predicted Relative Standard Deviation [PRSD(R) or $PRSD_R$]

The reproducibility relative standard deviation calculated from the Horwitz formula:

$$PRSD(R) = 2C^{-0.15}$$

where C is expressed as a mass fraction. *See* Table D1.

In spreadsheet notation: PRSD(R) = 2 * C ^(–0.15).

1.8 HorRat Value

The ratio of the reproducibility relative standard deviation calculated from the data to the PRSD(R) calculated from the Horwitz formula:

$$HorRat = RSD(R)/PRSD(R)$$

To differentiate the usual HorRat value calculated from reproducibility data from the HorRat value calculated from repeatability data, attach an R for the former and an r for the latter. But note that the denominator always uses the PRSD(R) calculated from reproducibility data because this parameter is more predictable than the parameter calculated from repeatability data:

$$HorRat(R) = RSD_R/PRSD(R)$$

$$HorRat(r) = RSD_r/PRSD(R)$$

Some expected, predicted relative standard deviations are given in Table D1.

2 *Acceptable HorRat Values*

2.1 For Interlaboratory Studies

HorRat(R): The original data developed from interlaboratory (among-laboratory) studies assigned a HorRat value of 1.0 with limits of acceptability of 0.5 to 2.0. The corresponding within-laboratory relative standard deviations were found to be typically 1/2 to 2/3 the among-laboratory relative standard deviations.

Table D2. Predicted relative standard deviations

Concentration (C)	$PRSD_R$, %	$PRSD_r$, %
100%	2	1
1%	4	2
0.01%	8	4
1 ppm	16	8
10 ppb	32	16
1 ppb	45	22

2.1.1 Limitations

HorRat values do not apply to method-defined (empirical) analytes (moisture, ash, fiber, carbohydrates by difference, etc.), physical properties or physical methods (pH, viscosity, drained weight, etc.), and ill-defined analytes (polymers, products of enzyme reactions).

2.2 For Intralaboratory Studies

2.2.1 Repeatability

Within-laboratory acceptable predicted target values for repeatability are given in Table D2 at 1/2 of PRSD(R), which represents the best case.

2.2.2 HorRat(r)

Based on experience and for the purpose of exploring the extrapolation of HorRat values to SLV studies, take as the minimum acceptability 1/2 of the lower limit ($0.5 \times 0.5 \approx 0.3$) and as the maximum acceptability 2/3 of the upper limit ($0.67 \times 2.0 \approx 1.3$).

Calculate HorRat(r) from the SLV data:

$$HorRat(r) = RSD(r)/PRSD(R)$$

Acceptable HorRat(r) values are 0.3–1.3. Values at the extremes must be interpreted with caution. With a series of low values, check for unreported averaging or prior knowledge of the analyte content; with a series of high values, check for method deficiencies such as unrestricted times, temperatures, masses, volumes, and concentrations; unrecognized impurities (detergent residues on glassware, peroxides in ether); incomplete extractions and transfers and uncontrolled parameters in specific instrumental techniques.

2.3 Other Limitations and Extrapolations

The HorRat value is a very rough but useful summary of the precision in analytical chemistry. It overestimates the precision at the extremes, predicting more variability than observed at the high end of the scale (C > ca 0.1; i.e., >10%) and at the low end of the scale (C < E-8; i.e., 10 ng/g; 10 ppb).

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ANNEX E
AOAC Method Accuracy Review

Accuracy of Method Based on Reference Material

Reference material (RM) used.—The use of RMs should be seen as integral to the process of method development, validation, and performance evaluation. RMs are not the only component of a quality system, but correct use of RMs is essential to appropriate quality management. RMs with or without assigned quantity values can be used for measurement precision control, whereas only RMs with assigned quantity values can be used for calibration or measurement trueness control. Method development and validation for matrices within the scope of the method is done to characterize attributes such as recovery, selectivity, "trueness" (accuracy, bias), precision (repeatability and reproducibility), uncertainty estimation, ruggedness, LOQ or LOD, and dynamic range. RMs should be chosen that are fit-for-purpose. When certified reference materials (CRMs) are available with matrices that match the method scope, much of the work involved in method development has already been completed, and that work is documented through the certificate. RMs with analyte values in the range of test samples, as well as "blank" matrix RMs, with values below or near detection limits, are needed.

Availability of RM.—Consideration needs to be given to the future availability of the chosen RM. Well-documented methods that cannot be verified in the future due to lack of material may lose credibility or be seen as inferior.

Fit to method scope.—Natural matrix CRMs provide the greatest assurance that the method is capable of producing accurate results for that matrix. When selecting an RM to perform a method validation, analysts should consider the method to material fit. An example of a good fit would be a method for specified organic molecules in infant formula and using an infant formula or powder milk RM. A poor fit would be a method for specified organic molecules in infant formula and using a sediment material.

Stability.—Providing a stable RM can be challenging where analytes are biologically active, easily oxidized, or interactive with other components of the matrix. CRM producers provide assurance of material stability, as well as homogeneity.CRMs are accompanied by a certificate that includes the following key criteria:

(*1*) Assigned values with measurement uncertainty and metrological traceability
(*2*) Homogeneity
(*3*) Stability, with the expiration date for the certificate
(*4*) Storage requirements
(*5*) Information on intended use
(*6*) Identity of matrix

For some RMs, such as botanical RMs, the source and/or authenticity can be a very important piece of information that should be included with the certificate. Even under ideal storage conditions, many analytes have some rate of change. Recertification may be done by the supplier, and a certificate reissued with a different expiration date and with certain analyte data updated or removed.

Definition of CRM.—Refer to the AOAC TDRM document for definitions from ISO Guide 30, Amd. 1 (2008), http://www.aoac.org/divisions/References.pdf.

Information on source of RM is available.—It is the responsibility of the material producer to provide reliable authentication of the RM and make a clear statement in the accompanying documentation. This should be an as detailed listing as possible, including handling of ingredients, identification of plant materials as completely as feasible (species, type, subtype, growing region), etc. This is comparable to other required information on an RM for judging its suitability for a specific application purpose (e.g., containing how much of the targeted analyte, stabilized by adding acid—therefore not suited for certain parameters/procedures, etc.).

Separate RM used for calibration and validation.—A single RM cannot be used for both calibration and validation of results in the same measurement procedure.

Blank RM used where appropriate.—Blank matrix RMs are useful for ensuring performance at or near the detection limits. These are particularly useful for routine quality control in methods measuring, for instance, trace levels of allergens, mycotoxins, or drug residues.

Storage requirements were maintained.—Method developers should maintain good documentation showing that the RM producer's recommended storage conditions were followed.

Cost.—The cost of ongoing method checks should be considered. Daily use of CRMs can be cost prohibitive. Monthly or quarterly analysis of these materials may be an option.

Concentration of analyte fits intended method.—Concentration of the analyte of interest is appropriate for standard method performance requirements (SMPRs).

Uncertainty available.—Every measurement result has an uncertainty associated with it, and the individual contributions toward the combined uncertainty arise from multiple sources. Achieving the target measurement uncertainty set by the customer for his/her problem of interest is often one of the criteria used in selecting a method for a given application. Estimation of measurement uncertainty can be accomplished by different approaches, but the use of RMs greatly facilitates this part of a method validation.

Demonstration of Method Accuracy when No Reference Material Is Available

If an RM is not available, how is accuracy demonstrated?

There are many analytes for which a CRM with a suitable matrix is not available. This leaves the analyst with few options. For some methods, there may be proficiency testing programs that include a matrix of interest for the analyte. Proficiency testing allows an analyst to compare results with results from other laboratories, which may or may not be using similar methods. Spiking is another technique that may be used. When alternative methods are available, results may be compared between the different methods. These alternatives do not provide the same level of assurance that is gained through the use of a CRM.

Spike recovery.—In the absence of an available CRM, one technique that is sometimes used for assessing performance is the spiking of a matrix RM with a known quantity of the analyte. When this method is used, it cannot be assumed that the analyte is bound in the same way as it would be in a natural matrix. Nevertheless, a certified blank RM would be the preferred choice for constructing a spiked material.

When preparing reference solutions, the pure standards must be completely soluble in the solvent. For insoluble materials in a liquid suspension or for powdered forms of dry materials, validation is required to demonstrate that the analyte is homogeneously distributed and that the response of the detection system to the analyte is not affected by the matrix or preparation technique. When a matrix material is selected for spiking, it should be reasonably

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characterized to determine that it is sufficiently representative of the matrix of interest. Spiked samples must be carried through all steps of the method. Many analytes are bound in a natural matrix and whether the spiked analyte will behave the same as the analyte in a natural matrix is unknown.

Other.—Use of a substitute RM involves the replacement of the CRM with an alternative matrix RM matching the matrix of interest as close as possible based on technical knowledge.

ANNEX F
Development and Use of In-House Reference Materials

The use of reference materials is a vital part of any analytical quality assurance program. However, you may have questions about their creation and use. The purpose of this document is to help answer many of these questions.

- What is a reference material?
- Why use reference materials?
- What certified reference materials are currently available?
- Why use an in-house reference material?
- How do I create an in-house reference material?
- How do I use the data from an in-house reference material?

What Is a Reference Material?

The International Organization for Standardization (ISO) defines a reference material as a "material or substance one or more of whose property values are sufficiently homogeneous and well established to be used for the calibration of an apparatus, the assessment of a measurement method, or for assigning values to materials" (1). In plain English, natural-matrix reference materials, such as those you might prepare for use in-house, can be used to validate an analytical method or for quality assurance while you're using your method to analyze your samples. (Natural-matrix materials are not generally used as calibrants because of the increased uncertainty that this would add to an analysis.) The assigned values for the target analytes of an in-house reference material can be used to establish the precision of your analytical method and, if used in conjunction with a CRM, to establish the accuracy of your method.

ISO defines a certified reference material (CRM) as a "reference material, accompanied by a certificate, one or more of whose property values are certified by a procedure which establishes traceability to an accurate realization of the unit in which the property values are expressed, and for which each certified value is accompanied by an uncertainty at a stated level of confidence" (1).

Why Use Reference Materials?

Certified reference materials can be used across the entire scope of an analytical method and can provide traceability of results to the International System of Units (SI). During method development, CRMs can be used to optimize your method. During method validation, they can be used to ensure that your method is capable of producing the "right" answer, and to determine how close your result is to that answer. During routine use, they can be used to determine within-day and between-day repeatability, and so demonstrate that your method is in control and is producing accurate results every time it is used.

Natural-matrix reference materials should mimic the real samples that will be analyzed with a method. They should behave just as your samples would during a procedure, so if you obtain accurate and precise values for your reference material, you should obtain accurate and precise values for your samples as well.

What Certified Reference Materials Are Currently Available?

CRMs are available from a number of sources, including (but not limited to):

- American Association of Cereal Chemists (AACC)
- American Oil Chemists Society (AOCS)
- International Atomic Energy Agency (IAEA)
- Institute for Reference Materials and Measurements (IRMM)
- LGC Promochem
- National Institute of Standards and Technology (NIST)
- National Research Council Canada (NRC Canada)
- UK Food Analysis Proficiency Assessment Program (FAPAS)

A number of websites provide general overviews and catalogs of producers' and distributors' reference materials:

http://www.aocs.org/tech/crm/
http://www.comar.bam.de
http://www.erm-crm.org
http://www.iaea.org/oregrammeslaqcs
http://www.aaccnet.org/checksample
http://www.irmm·ire.be/mrm.html
http://www.lgcpromochem.com
http://www.naweb.iaea.org/nahu/nmrm/
http://www.nist.gov/srm
http://www.fapas.com/index. cfm
http://www.virm.net.

Because new reference materials are produced regularly, it is important to check these websites to determine what is currently available.

Why Use an In-House Reference Material?

There are many benefits to the use of a CRM. CRMs have been prepared to be homogeneous and, if stored under the proper conditions, stable. You are provided with a certified value as well as the statistical data for theconcentration of your analyte; this is about as close as you can come to knowing the true value of the concentration of the analyte. The material has been tested by experienced analysts in leading laboratories, so you have the security of knowing that your method is generating values similar to those generated in other competent laboratories. The CRMs from the sources mentioned above are nationally and/or internationally recognized, so when you obtain acceptable results for a CRM using your analytical method, you give credibility to your methodology and traceability to your results.

But there are some drawbacks associated with CRMs. Unfortunately, many analyte/matrix combinations are not currently available. When testing food products for nutrient content, for example, a laboratory can be asked to analyze anything that might be found in a kitchen or grocery store. Reference materials that represent all of the types of foods that need to be tested are not available, and most CRMs are certified for a limited number of analytes. It is important to match the reference material matrix to your sample matrix. (Food examples dominate the discussion below, but the same processes apply to the development of in-house RMs in other areas of analytical chemistry.)

To demonstrate the applicability of an analytical method to a wide variety of food matrices, AOAC INTERNATIONAL's Task

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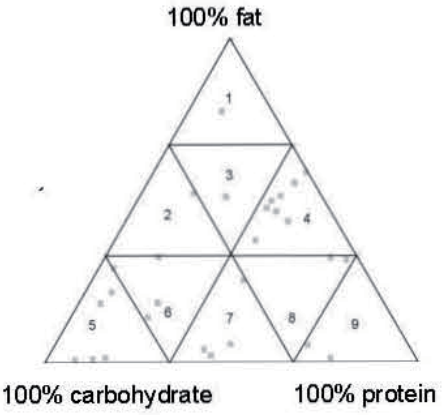

Force on Methods for Nutrition Labeling developed a triangle partitioned into sectors in which foods are placed based on their protein, fat, and carbohydrate content (2, 3). Since ash does not have a great impact on the performance of an analytical method for organic-material foods, and water can be added or removed, it can be assumed that the behavior of an analytical method is determined to large extent by the relative proportions of these proximates. AOAC INTERNATIONAL anticipated that one or two foods in a given sector would be representative of other foods in that sector and therefore would be useful for method assessment. Similarly, one or two reference materials in a given sector (or near each other in adjacent sectors) should be useful for quality assurance for analyses involving the other foods in the sector. The positions of many of the food-matrix CRMs from the sources listed above are shown in the triangle and are provided in the list.

These food-matrix reference materials are spread through all sectors of the triangle, thereby making it likely that you can find an appropriate CRM to match to your samples. Ultimately, however, the routine use of a CRM can be cost prohibitive, and is not really the purpose of CRMs. For example, in order to use NIST's Standard Reference Material (SRM) 2387 Peanut Butter for all mandatory nutrition labeling analyses, you could buy one sales unit (three jars, each containing 170 g material) for $649 (2009 price). If you charge your customer about $1000 for analysis of all mandatory nutrients in a test material, the control material would account for more than 60% of your fees. Therefore, many laboratories have found it more cost-effective to create in-house reference materials for routine quality control and characterize them in conjunction with the analysis of a CRM (4). You can prepare larger quantities of a reference material by preparing it in-house, and you have more flexibility in the types of matrices you can use. There are not many limitations on what can be purchased.

How Do I Create an In-House Reference Material?

There are basically three steps to preparing an in-house reference material: selection (including consideration of homogeneity and stability), preparation, and characterization. Additional guidance through these steps can be provided from TDRM as well as in ISO Guides 34 (5) and 35 (6).

References

(1) JCGM 200:2008, *International vocabulary of metrology—Basic and general concepts and associated terms (VIM)*, International Bureau of Weights and Measures (www.bipm.org)

Sector	RM No.	Matrix
	NIST 1563	Coconut oil
1	NIST 3274	Fatty acids in botanical oils
1	NIST 3276	Carrot extract in oil
1	LGC 7104	Sterilized cream
2	NIST 2384	Baking chocolate
3	NIST 2387	Peanut butter
4	NIST 1546	Meat homogenate
4	LGC 7106	Processed cheese
4	LGC 7000	Beef/pork meat
4	LGC 7150	Processed meat
4	LGC 7151	Processed meat
4	LGC 7152	Processed meat
4	SMRD 2000	Fresh meat
4	LGC 7101	Mackerel paste
4	LGC QC1001	Meat paste 1
4	LGC QC1004	Fish paste 1
5	BCR-382	Wleat flour
5	BCR-381	Rye flour
5	LGC 7103	Sweet digestive biscuit
5	LGC 7107	Madeira cake
5	LGC QC1002	Flour 1
6	NIST 1544	Fatty acids
6	NIST 1548a	Typical diet
6	NIST 1849	Infant/adult nutritional formula
6	LGC 7105	Rice pudding
7	LGC 7001	Pork meat
7	NIST 1566b	Oyster tissue
7	NIST 1570a	Spinach leaves
7	NIST 2385	Spinach
8	NIST 1946	Lake trout
8	LGC 7176	Canned pet food
9	NIST 1974a	Mussel tissue
9	NIST 3244	Protein powder

(2) Wolf, W.R., & Andrews, K.W. (1995) *Fresenius' J. Anal. Chem.* **352**, 73–76

(3) Wolf, W.R. (1993) *Methods of Analysis for Nutrition Labeling*, D.R. Sullivan & D.E. Carpenter (Eds), AOAC INTERNATIONAL, Gaithersburg, MD

(4) European Reference Materials (2005) *Comparison of a Measurement Result with the Certified Value*, Application Note 1

(5) *ISO Guide 34 General Requirements for the Competence of Reference Material Producers* (2009) 2nd, International Organization for Standardization, Geneva, Switzerland

(6) *Guide 35 Certification of Reference Materials—General and Statistical Principles* (2006) International Organization for Standardization, Geneva, Switzerland

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