



VDSP – Standardisation Issues with 25-hydroxyvitamin D

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For the Vitamin D Standardization Program (VDSP)

Vitamin D: Analytical and Clinical Stories

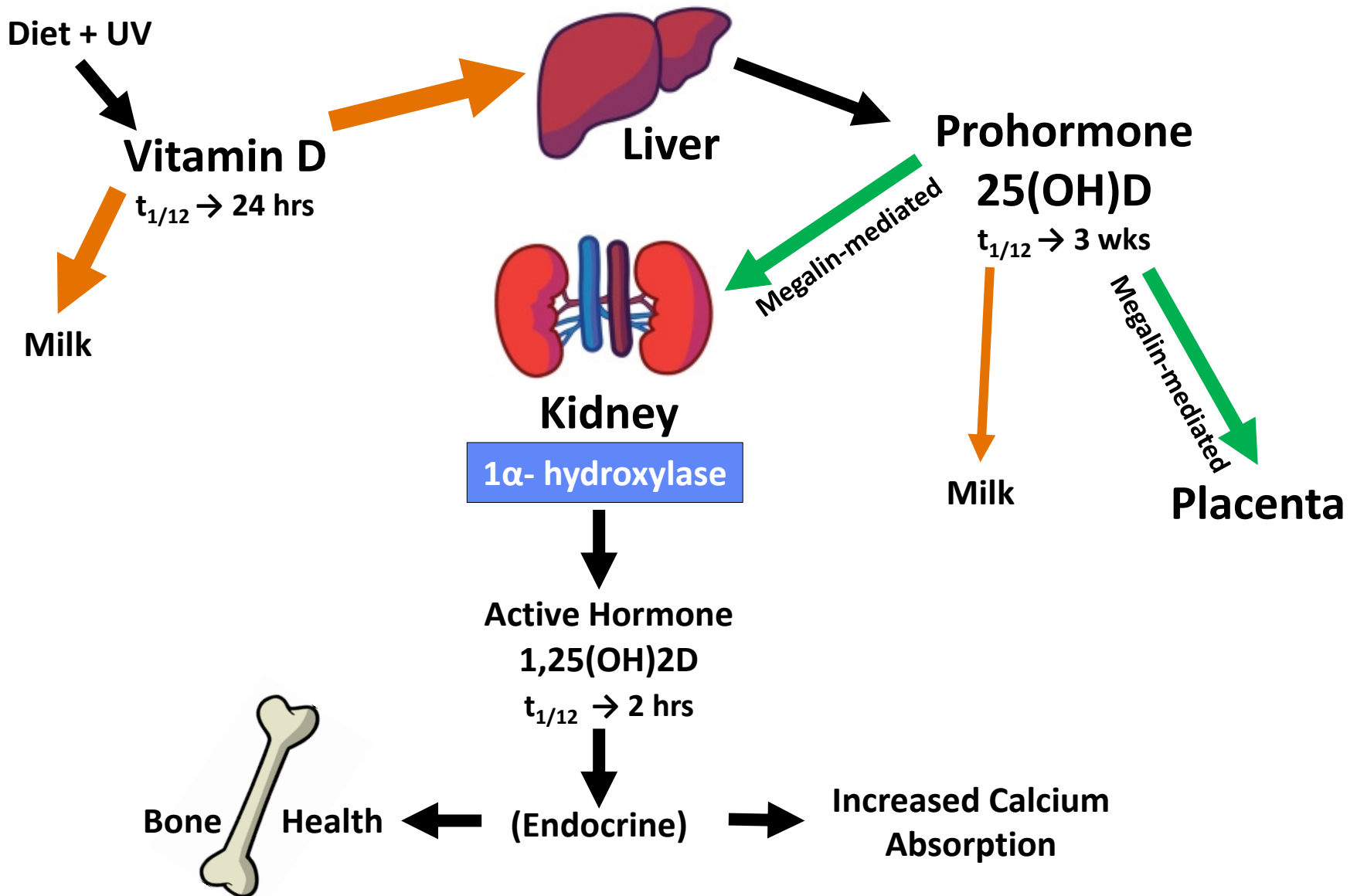
7th July 2016

**Imperial College, South Kensington Campus
London, UK**

Thank you!

- I would like to thank Dr. Walker for her kind introduction.
- I would like to thank Graham Carter and all of the meeting organizers for their kind invitation.
- Finally, I would like to thank, as well, Graham, Julia and Emma for their support of the Vitamin D Standardization Program (VDSP).

Vitamin D Metabolism and Tissue Homeostasis



Vitamin D Status Measurement

Total 25-Hydroxyvitamin D or 25(OH)D

- Total 25(OH)D is defined as

$$\text{Total 25(OH)D} = 25(\text{OH})\text{D}_2 + 25(\text{OH})\text{D}_3^*$$

- Units: ng/mL or nmol/L where:

$$\text{ng/ml} * 2.5 \approx \text{nmol/L}$$

- * Assumes that Vitamin D₂ and D₃ are of equal biological value.



Outline

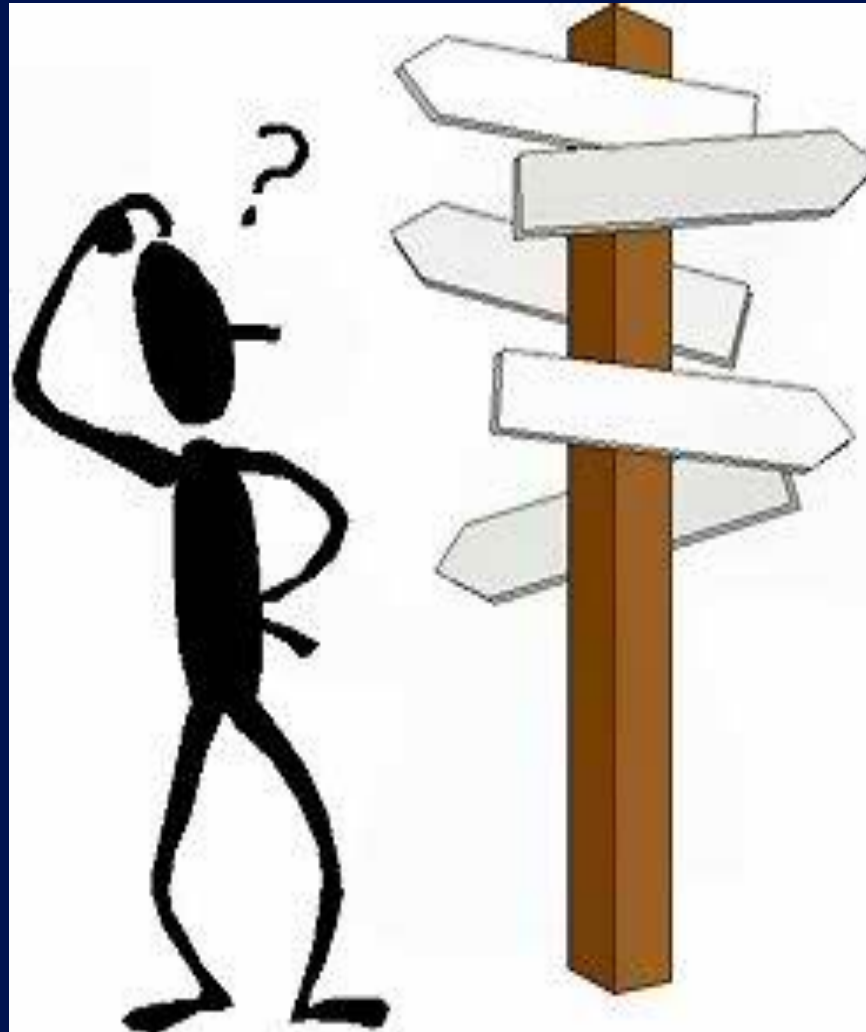
- Chaos
- Vitamin D Standardization Program (VDSP)
- Going Forward

Chaos

- ◆ Huge numbers of people either are, or are not vitamin D deficient
- ◆ This deficiency either is, or is not, causing disease thereby reducing quality and quantity of life
- ◆ The vitamin D field is in chaos.....



How Can Patients, Physicians & Policy Makers NOT be Confused?



Source of Chaos: The Problem

0021-972X/04/\$15.00/0
Printed in U.S.A.

The Journal of Clinical Endocrinology & Metabolism 89(7):3152-3157
Copyright © 2004 by The Endocrine Society
doi: 10.1210/jc.2003-031979

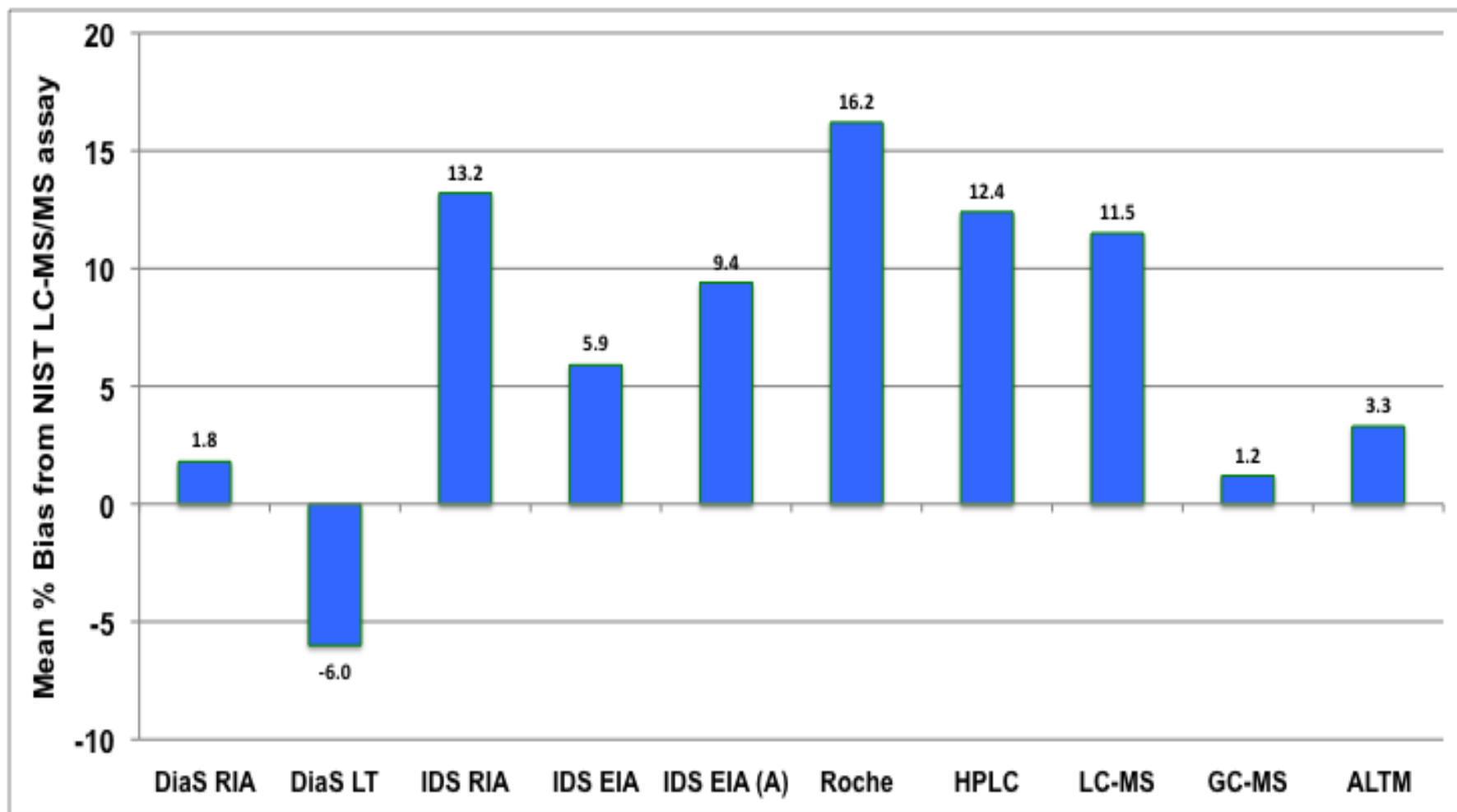
Assay Variation Confounds the Diagnosis of Hypovitaminosis D: A Call for Standardization

N. BINKLEY, D. KRUEGER, C. S. COWGILL, L. PLUM, E. LAKE, K. E. HANSEN, H. F. DeLUCA, AND M. K. DREZNER

N. Binkley et al. The Journal of Clinical Endocrinology & Metabolism 2004;89(7):3152-7



Deviation (% bias) from NIST Reference Measurement Procedure (LC-MS/MS). DEQAS 2008.



Source: Carter GD. Current Drug Topics. 2011;12(1):19-28.



What is Standardization?

Standardized laboratory measurement of 25-hydroxyvitamin D is:

Accurate and comparable to Gold Standard *Reference Measurement Procedures (RMPs)** over time, location, and laboratory procedure.

* Tai S et al. *Anal Chem* 2010;82:1942-1949.

* Stepman HCM et al. *Clin Chem* 2011;57:441-448.

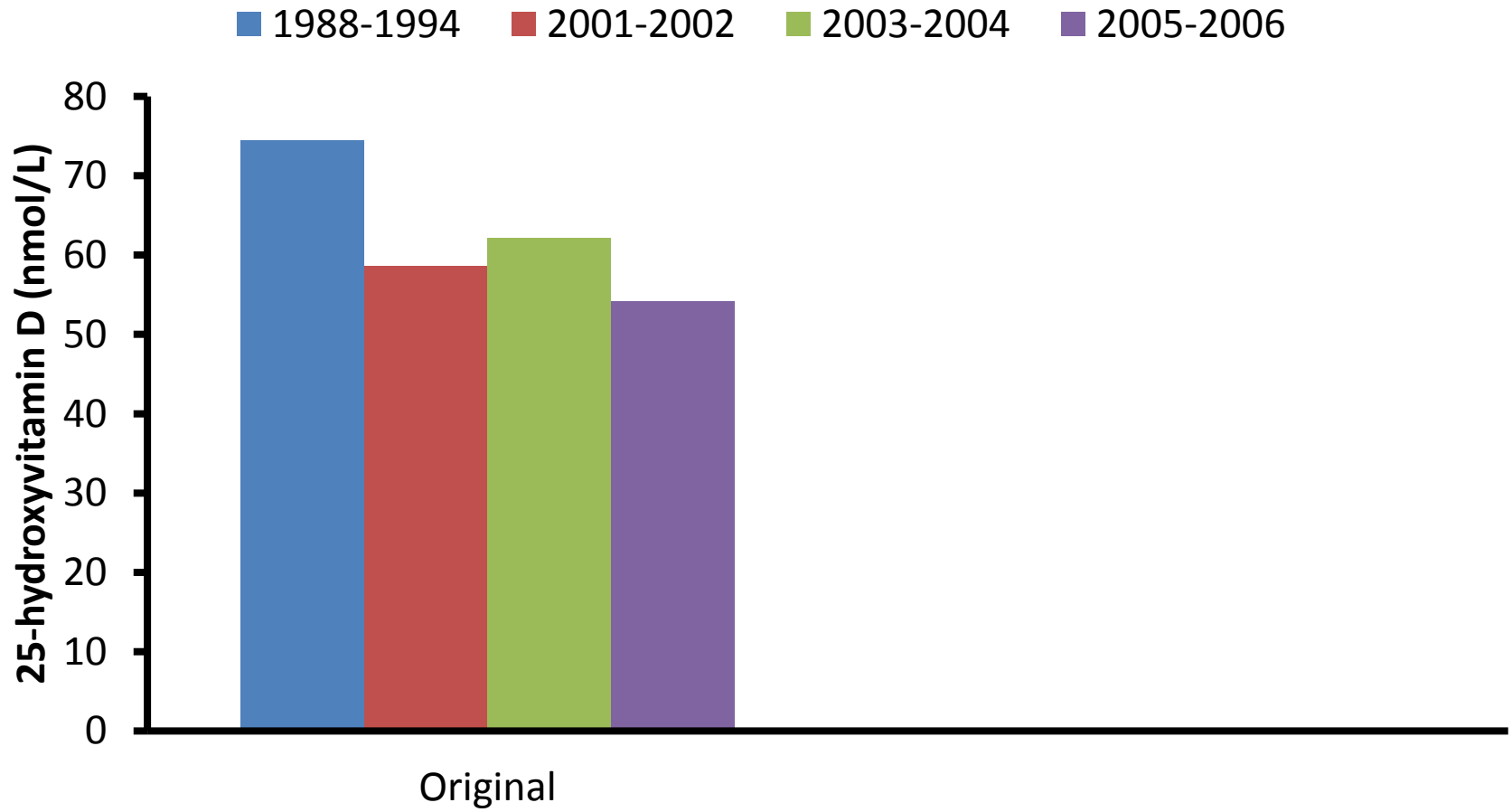


Effects of Standardization

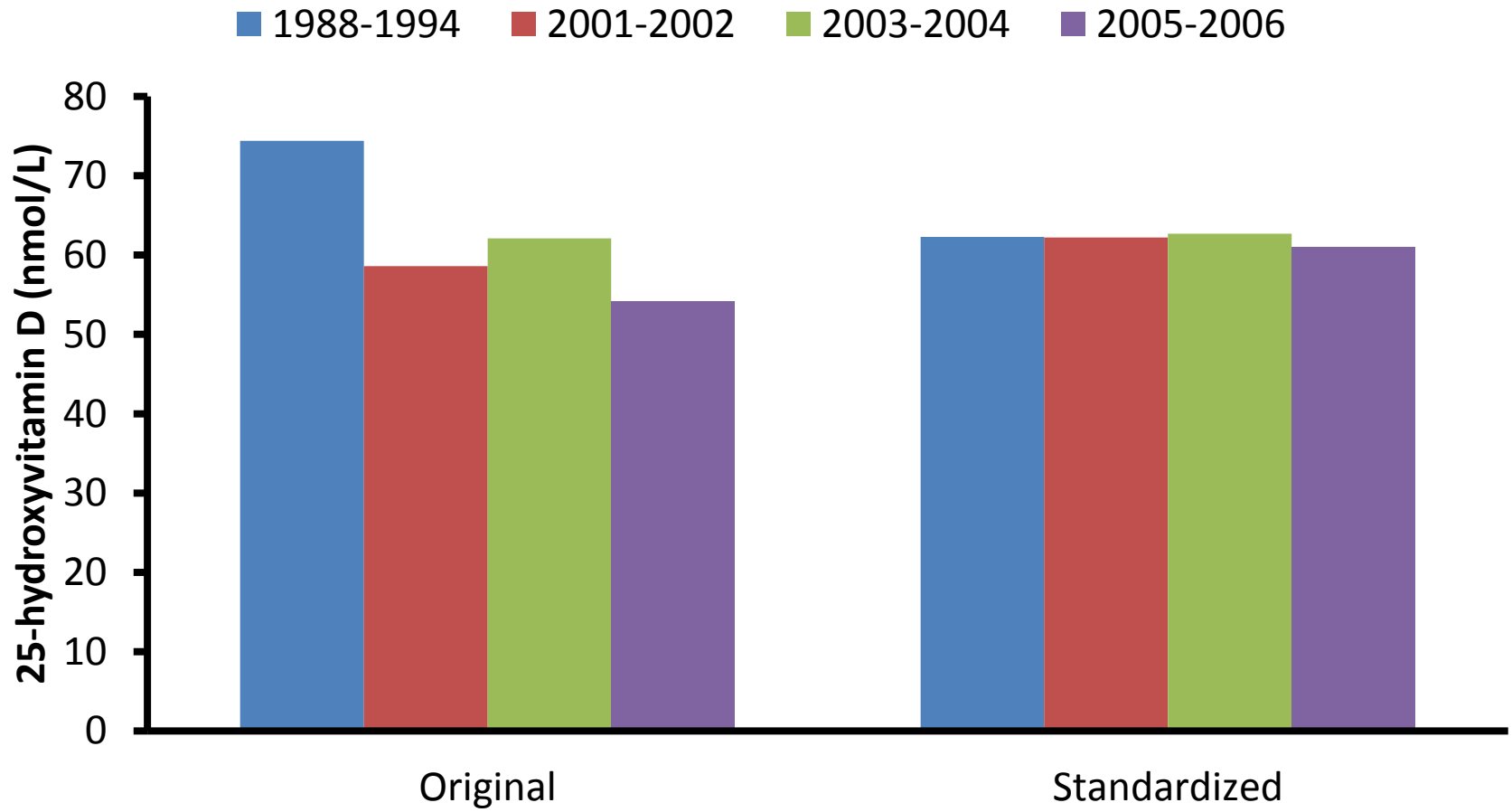
All Laboratories report true value – based on NIST, Ghent & CDC RMPs which permits:

- Pooling of research results
- Evidenced-based guidelines
- Informed decision making by physicians, policymakers and others

Trends in Original and Standardized 25(OH)D



Trends in Original and Standardized 25(OH)D





Vitamin D Standardization Program (VDSP): An Overview



Vitamin D Standardization Program (VDSP)*

Goal: Promote the standardized laboratory measurement of 25-hydroxyvitamin D – a measure of vitamin D status – in order to improve clinical and public health practice worldwide.

*Sempos C et al. Scand J Clin & Lab Inv 2012;72(Suppl 243): 32-40.

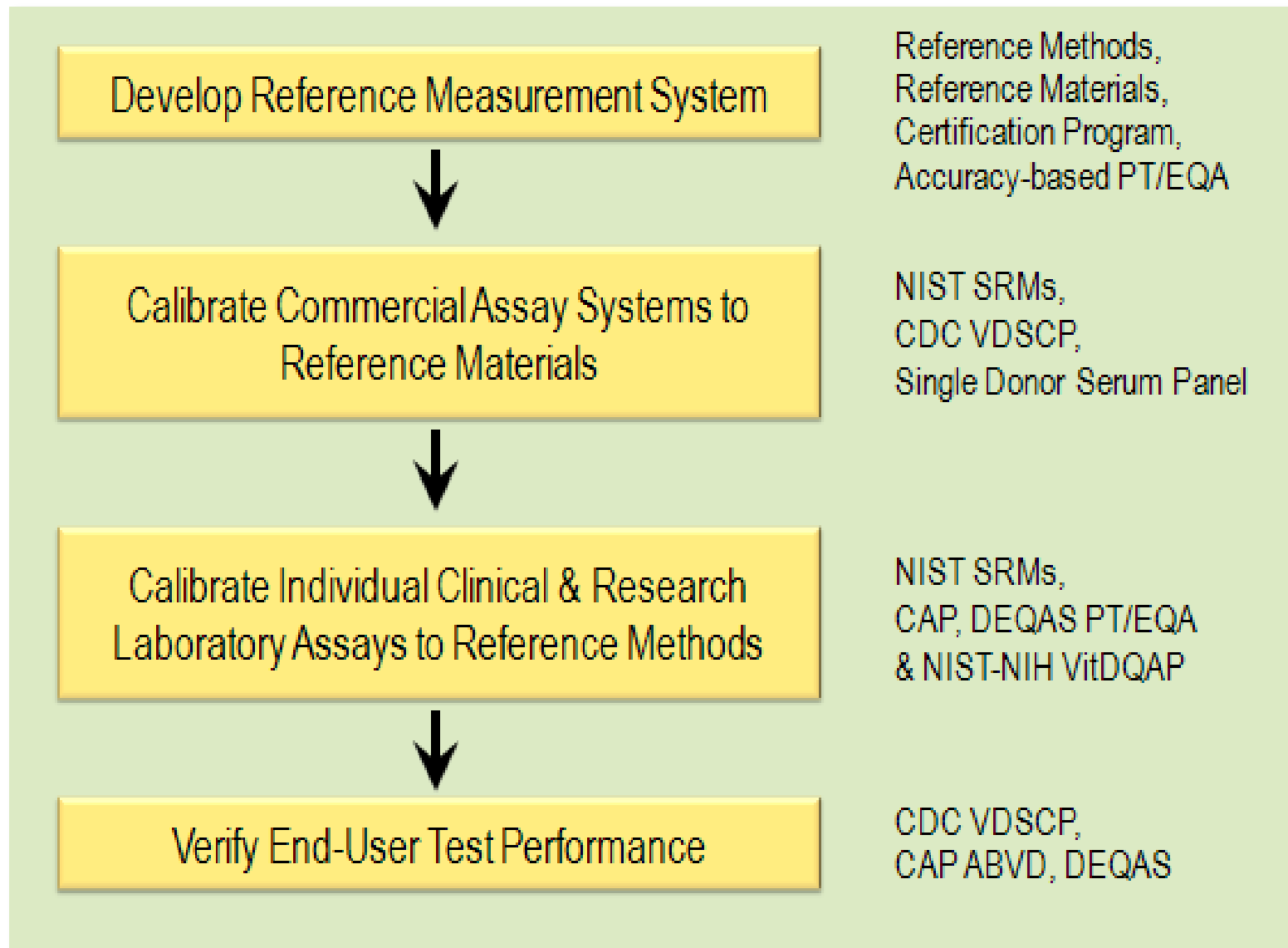
Note: 25-hydroxyvitamin D is abbreviated as 25(OH)D



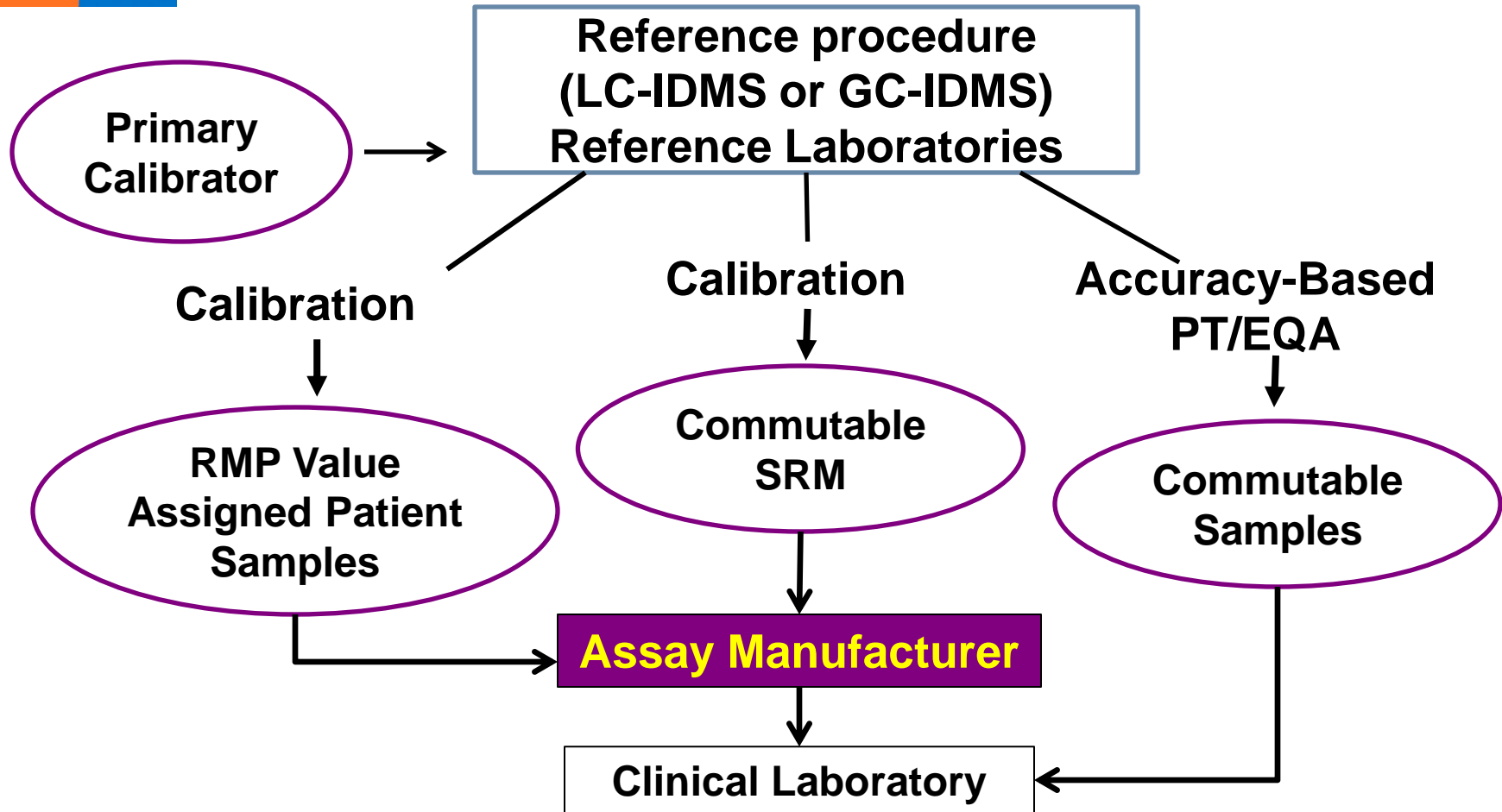
VDSP Reference Measurement System Components

- NIST, Ghent & CDC RMPs
- NIST Standard Reference Materials (SRM)
- Performance Standards
- CDC Vitamin D Standardization-Certification Program
- Accuracy-Based Performance Testing (PT)
- Standardizing completed studies

VDSP: Steps to Standardization



VDSP: Calibration of Individual Assays



* Adapted from: Myers G. Steroids 2008;73:1293-1296

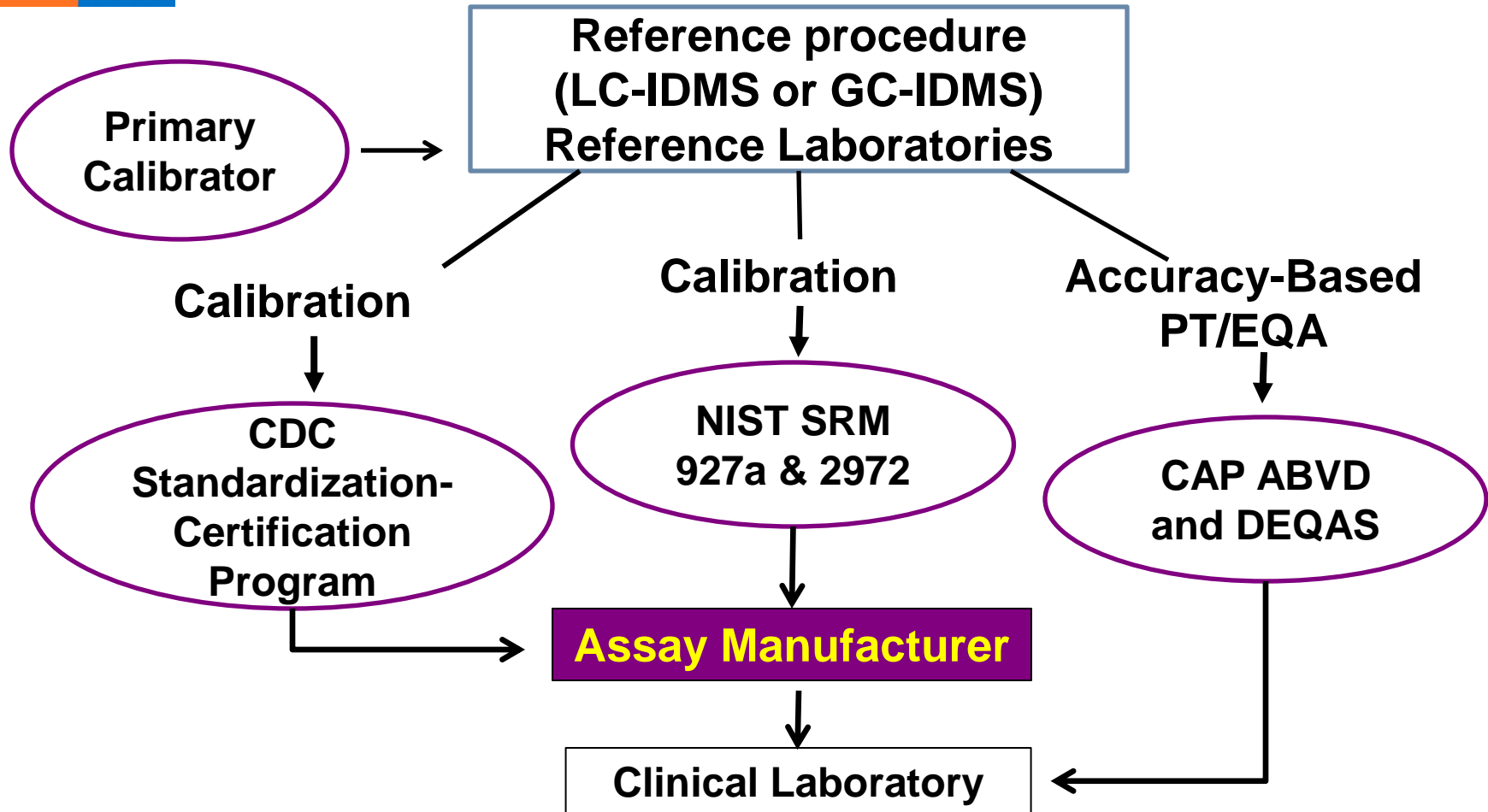


VDSP Performance Limits Based on Biological Variation*

Measurements	CV (%)	Mean Bias (%)
Reference Labs	$\leq 5\%$	$\leq 1.7\%$
“Routine” Labs	$\leq 10\%$	$\leq 5\%$

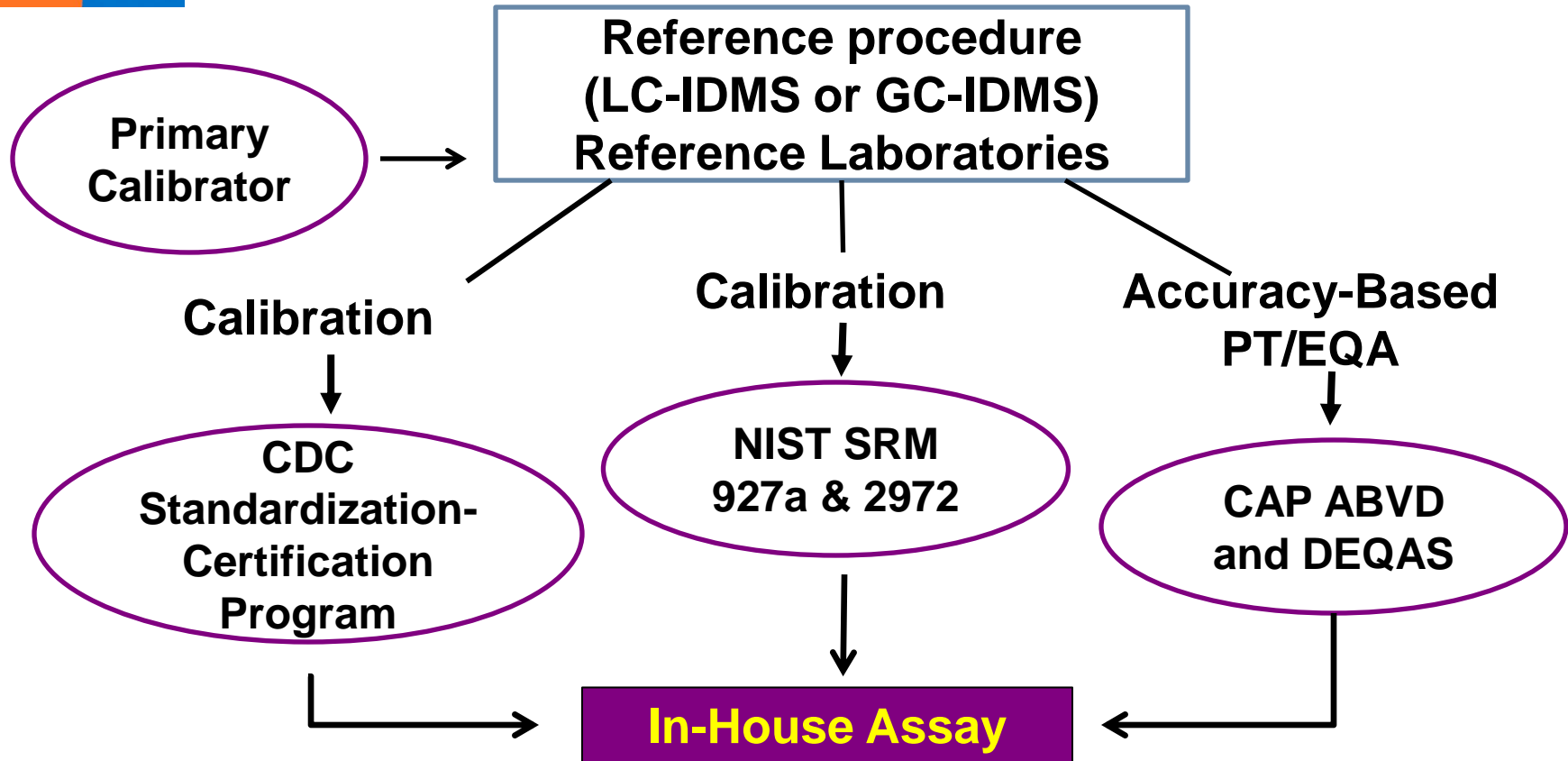
*Stöckl D et al. Clin Chim Acta 2009;408:8-13

VDSP: Calibration of Individual Assays



* Adapted from: Myers G. Steroids 2008;73:1293-1296

VDSP: Calibration of In-House Assays



* Adapted from: Myers G. Steroids 2008;73:1293-1296



Steps You Can Take Now To Achieve Standardization

- Use NIST SRMs to calibrate assays and serum pools, and as trueness controls
- CDC Vitamin D Standardization Certification Program – Participation needed by
 - Commercial assay manufacturers
 - Commercial and large clinical laboratories
 - Research laboratories



Steps You Can Take Now To Achieve Standardization

- Participate in CAP and/or DEQAS accuracy-based EQA programs:
 - Small clinical laboratories
 - Research laboratories
- Run serum-based SRM 972a (DEQAS) samples with research study samples – trueness controls
- Use EQA results to monitor accuracy and precision (mean bias) over time



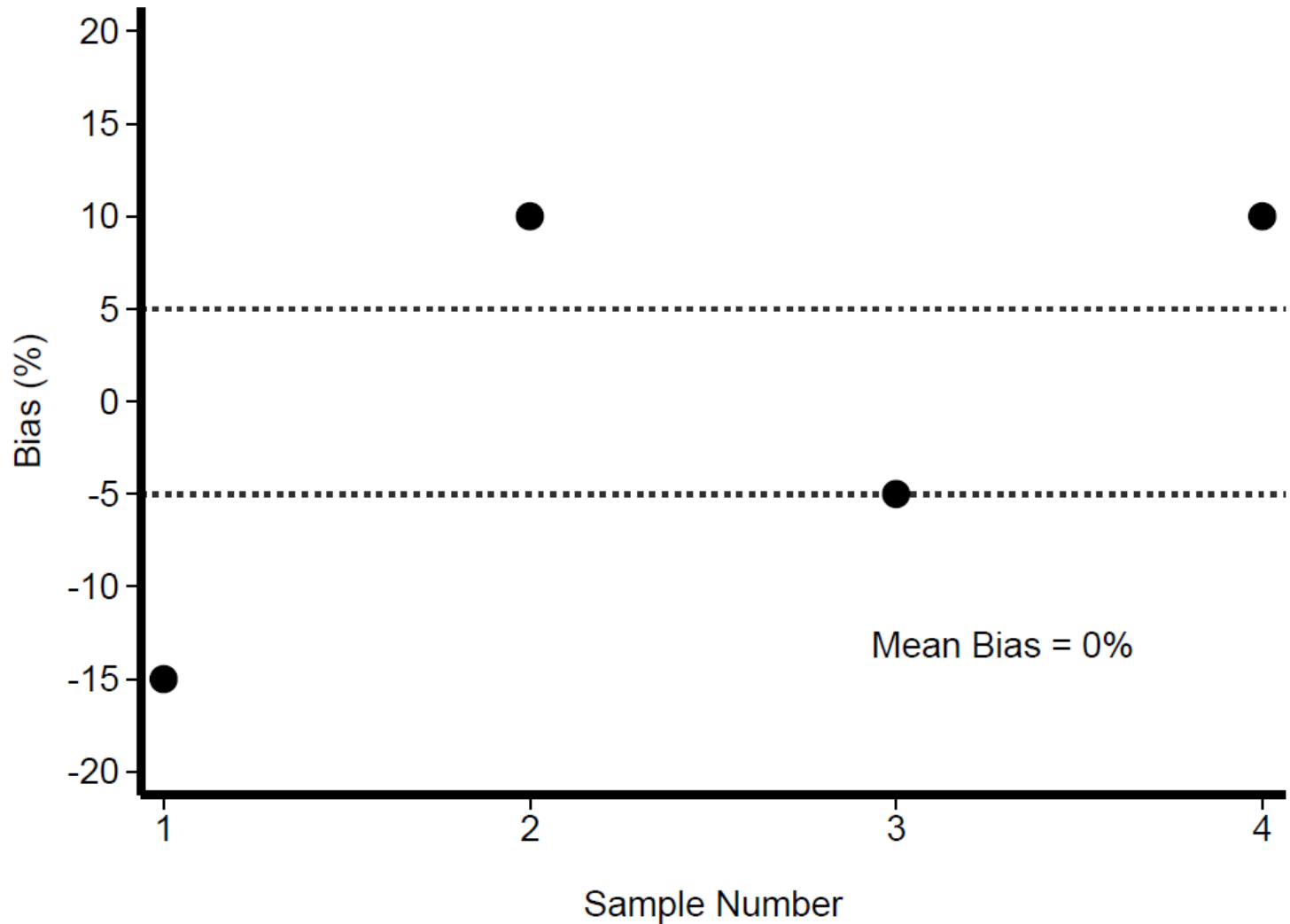
VDSP Performance Limits Based on Biological Variation*

Measurements	CV (%)	Mean Bias (%)
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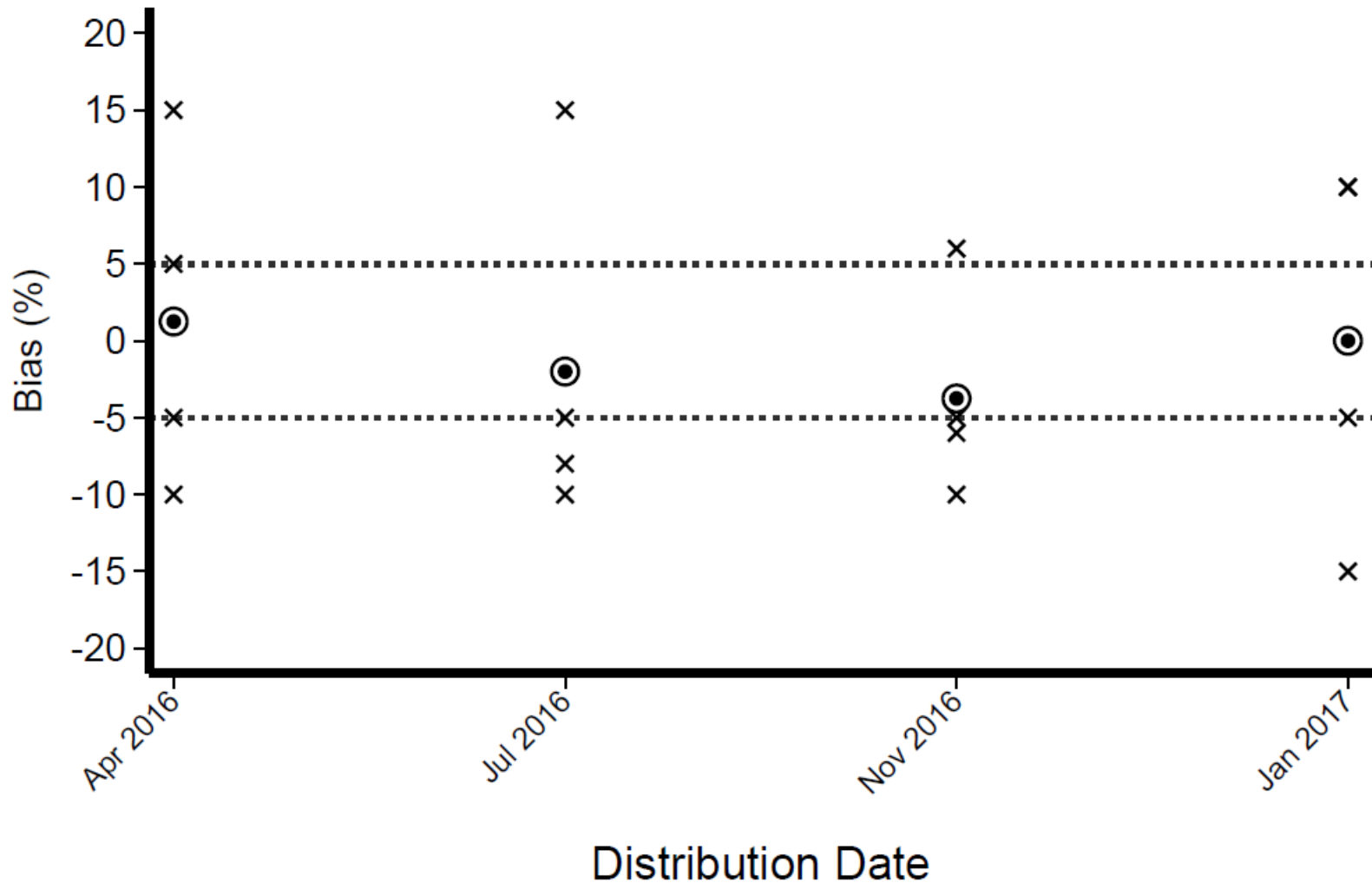
*Stöckl D et al. Clin Chim Acta 2009;408:8-13

Laboratory X: DEQAS Results

January 2017 Distribution



Laboratory X: DEQAS Results April 2016 - January 2017 Distributions





Going Forward

Certified Laboratories and Assays &
Recent Data from DEQAS



CDC Certified Laboratories as of November 2014

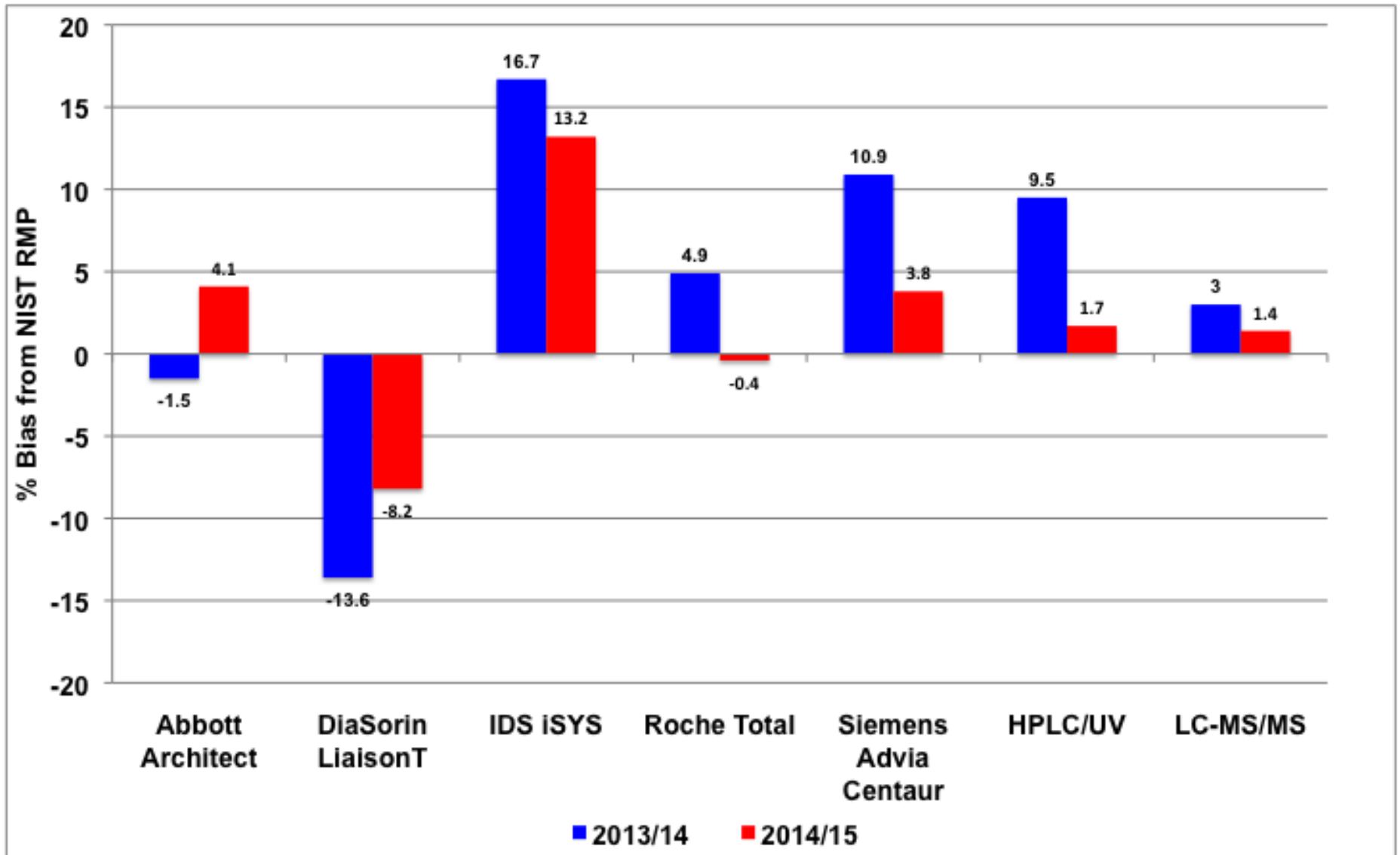
N	Participant	Measurement Principle	Method Identifier
1	DiaSorin	Chemiluminescence Immunoassay	LIAISON® 25(OH)D
2	Quest Diagnostics	LC-MS/MS	Total 25(OH)D
3	U. Western Australia	LC-MS/MS	Total 25(OH)D
4	Covance Central Lab. Services, Inc.	LC-MS/MS	Total 25(OH)D
5	LabCorp	LC-MS/MS	Total 25(OH)D
6	U of Leige, Belgium	LC-MS/MS	Total 25(OH)D
7	Mayo Clinic	LC-MS/MS	Total 25(OH)D



CDC Certified Laboratories as of November 2014

N	Participant	Measurement Principle	Method Identifier
8	Siemens	Chemiluminescence Immunoassay	ADVIA Centaur®
9	Path Assoc Med Lab, LLC	LC-MS/MS	Total 25(OH)D
10	IDS	Immunoassay	IDS-iSYS
11	IDS	Immunoassay	25(OH)D EIA
12	UCC	LC-MS/MS	Total 25(OH)D
13	Douglas Hanly Moir Pathology	LC-MS/MS	Total 25(OH)D

Mean Deviation (%Bias) of 25-OHD assays from the NIST Reference Measurement Procedure: DEQAS Last Two Distribution Cycles





Finally, Ask Yourself?

- What's your assay's CV? Is it $\leq 10\%$
- What's your assay's mean Bias? Is it $\leq 5\%$ -
More importantly, what is the proportion of
Bias estimates between $\pm 5\%$?
- Proportion between $\pm 5\%$ is the index of
standardization progress from PT/EQA.



VDSPP Contributors

- **ODS: Overall Coordination**

- Paul Coates
- Joseph Betz
- Claudia Faigen
- Megan Lyons
- Joyce Merkel
- Mary Frances Picciano*
- Christopher Sempos**
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- Anne Thurn
- Elizabeth Yetley

- **International Organizations:**

- **AACC** - Gary Myers
- **IFCC** - Ian Young
- **CAP** – Andrew Hoofnagle
- **DEQAS**
 - Graham Carter
 - Julia Jones
 - Emma Walker

* Deceased

** VDSPP Coordinator

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- Carolyn Burdette
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- Katrice Lippa
- Karen Phinney
- Susan Tai

- **Belgium: Ghent University**

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- Linde De Grande
- Katleen Van Uytfanghe

- **CDC Standardization-Certification Program**

- Hubert Vesper
- Julianne Botelho



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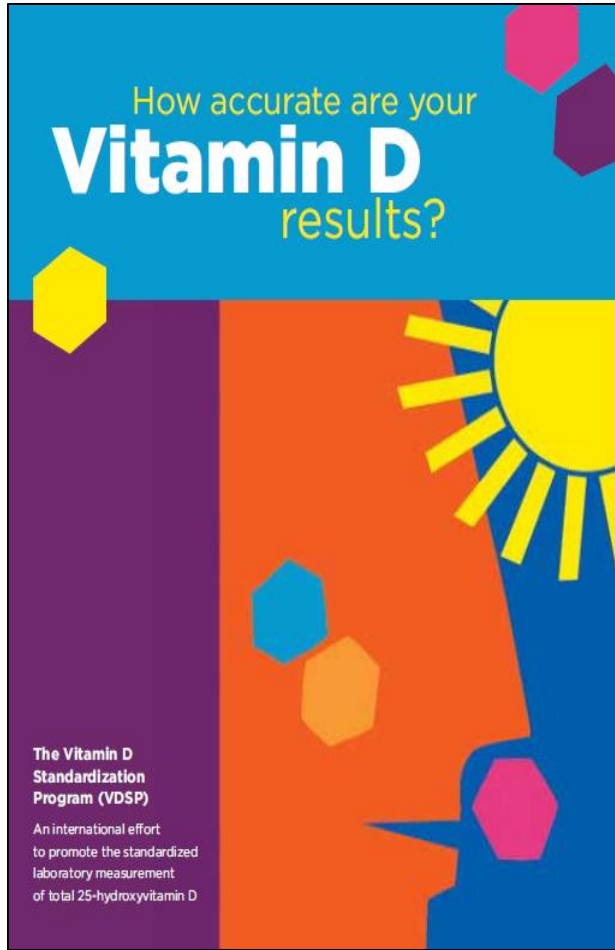
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Thank you!

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Join the VDSP effort!

<http://ods.od.nih.gov/VitaminD>



**Sign up for the
VDSP e-mail list!**

Email: VDSP@mail.nih.gov