SIEMENS

Urgent Field Safety Notice

CC 16-14.A.OUS

October, 2016

ADVIA Centaur®
ADVIA Centaur® XP
ADVIA Centaur® XPT

Vitamin D Total– Change in Correlation Between Serum and Plasma Specimen Tubes

Our records indicate that your facility may have received the following product:

Table 1. ADVIA Centaur Systems Affected Product(s)

Assay	Test Code	Catalog Number	Siemens Material Number (SMN)	Kit Lots Ending In	Expiration Date	Manufacturing Date
Vitamin D Total 100 Tests	VitD	10699201	10699201	065 066 067 068 069 070	2016/11/09 2017/01/30 2017/03/11 2017/04/23 2017/07/21 2017/08/25	2015/10/09 2015/12/30 2016/02/11 2016/03/23 2016/06/21 2016/07/25
Vitamin D Total 500 Tests	VitD	10699533	10699533	065 066 067 068 069 070	2016/11/09 2017/01/30 2017/03/11 2017/04/23 2017/07/21 2017/08/25	2015/10/09 2015/12/30 2016/02/11 2016/03/23 2016/06/21 2016/07/25

Reason for Correction

Siemens Healthcare Diagnostics has confirmed a change in correlation between serum and plasma specimen tubes with the ADVIA Centaur Vitamin D Total assay as compared to Instructions for Use (IFU). Newly evaluated data demonstrate a Deming regression slope between 0.93 and 0.95 for plasma samples as compared to serum samples whereas, the specimen collection comparison data provided in the IFU indicates a linear regression slope of up to 1.09.[1] This Urgent Field Safety Notice applies to all in-date lots of ADVIA Centaur Vitamin D Total as shown in Table 1 and all future lots.

The latest study used 70 matched specimens drawn in 12 different tube types. Specimen tube types included Greiner tubes (Lithium Heparin and Sodium Heparin), Covidien tubes (Serum, Serum Separator and EDTA K3) and Becton-Dickinson tubes (Sodium and Lithium Heparin, EDTA K2 and K3 and Serum and Serum Separator). 25(OH)vitamin D values ranged from 4.7 – 137 ng/mL (11.7 – 342 nmol/L). Refer to Table 2 below for Deming regression statistics of the different tube types. Based on

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statistical equivalence, the data generated for each tube type from the different manufacturers has been combined. The EDTA tube type includes data from K2 and K3 tubes. Internal data shows that human plasma collected in EDTA, lithium heparin or sodium heparin tube types reported a mean bias of negative 16 to 20% versus serum across the assay range. Biases between serum and plasma tube types may vary depending on the specimen tube manufacturer.

Table 2. Deming Regression Analysis Using Serum as the Reference

Tube Type	Slope	Intercept ng/mL	Intercept nmol/L	R
Serum Separator	0.98	0.06	0.15	0.996
EDTA	0.95	-4.82	-12.1	0.989
Lithium Heparin	0.94	-3.38	-8.45	0.993
Sodium Heparin	0.93	-3.08	-7.70	0.991

Siemens plans to update the Instructions for Use. Availability of updated Instructions for Use is dependent on local regulatory requirements.

This change in correlation was further evaluated for potential impact at different concentrations of vitamin D. Table 3 below provides the predicted vitamin D values and the 95% Confidence Intervals for each tube type at 25(OH)vitamin D concentrations of 20, 30 and 100 ng/mL (50, 75 and 100 nmol/L).

Table 3. Percent Bias and 95% Confidence Intervals at 3 Concentrations of 25(OH)Vitamin D When Compared to Serum Samples

Tube Type		Vitamin D 20 ng/mL (50 nmol/L)	Vitamin D 30 ng/mL (75 nmol/L)	Vitamin D 100 ng/mL (250 nmol/L)
Serum Separator	Average Bias	-2.0%	-2.1%	-2.3%
	95% Confidence Interval of Bias	-5.2% to 1.1%	-4.2% to -0.1%	-4.7% to 0.2%
EDTA	Average Bias	-28.9%	-20.9%	-9.6%
	95% Confidence Interval of Bias	-33.3% to -24.5%	-23.9% to -17.8%	-14.8% to -4.4%
Lithium Heparin	Average Bias	-23.0%	-17.3%	-9.5%
	95% Confidence Interval of Bias	-26.5% to -19.4%	-19.8% to -14.9%	-11.9% to -7.0%
Sodium Heparin	Average Bias	-22.3%	-17.2%	-10.0%
	95% Confidence Interval of Bias	-26.3% to -18.4%	-19.9% to -14.5%	-13.7% to -6.3%

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The IFUs suggests the following categories of Vitamin D status based on a review of available literature. [2-6]

Table 4. Suggested Categories of Vitamin D Status

Vitamin D Status	Range, Adult ng/mL (nmol/L)	Range, Pediatric ng/mL (nmol/L)
Deficiency D	< 20 ng/mL (<50 nmol/L)	<15 ng/mL (<37.5 nmol/L)
Insufficiency	20 - < 30 ng/mL (50 - < 75 nmol/L)	15 - < 20 ng/mL (37.5 - < 50 nmol/L)
Sufficiency	30 – 100 ng/mL (75 – 250 numol/L)	20 – 100 ng/mL (50 – 250 nmol/L)

In addition to the change in correlation observed, Siemens Healthcare has also identified that the current IFU incorrectly states that Becton-Dickinson tubes were used to generate the existing tube type data. The tube type data currently in the IFU were generated with Covidien and Greiner sample tubes.

The assay is not available on the ADVIA Centaur CP system.

Risk to Health

The bias observed between serum and plasma samples has the potential to impact interpretation of vitamin D status should a plasma tube type be used in a patient whose 25-OH vitamin D level is at or near the cutoffs for Deficient versus Insufficient or Insufficient versus Sufficient. When this issue occurs, the potential exists to initiate unnecessary vitamin D supplementation and/or additional monitoring of vitamin D levels with negligible risk to health. The biases observed would not lead to missed vitamin D deficiency or toxicity. Siemens is not recommending a review of previously generated results.

Actions to be Taken by the Customer

- Customers may continue to use the ADVIA Centaur Vitamin D Total assay with both serum and plasma specimen types, however, they should consider the bias when evaluating samples in different tube types.
- Complete and return the Field Correction Effectiveness Check Form attached to this letter within 30 days
- Please review this letter with your Medical Director.

Please retain this letter with your laboratory records, and forward this letter to those who may have received this product.

We apologize for the inconvenience this situation may cause. If you have any questions, please contact your Siemens Customer Care Center or your local Siemens technical support representative.

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Product availability may vary from country to country and is subject to varying regulatory requirements. Due to local regulations, the ADVIA Centaur XPT is not available in all countries.

References

1.Clinical and Laboratory Standards Institute (CLSI) EP09-A3 Measurement Procedure Comparison and Bias Estimation Using Patient Samples; Approved Guideline-3rd Edition August 2013.

2.Holick MF. Vitamin D Deficiency. *N Engl J Med.* 2007;357:266–81.

3.Holick MF. MrOs is D-ficient. *J Clin Endocrinol Metab*. 2009;94(4):1092–3.

4.Rollins G. Vitamin D Testing–What's the Right Answer? Labs Grapple with Confusing Analytics, Evidence. *Clinical Laboratory News.* July 2009;35(7): 1,6.

5.Freeman R. Vitamin D: The sunshine hormone. How and when to treat deficiencies. *Menopausal Medicine.* May 2009; S8–11.

6.Misra M, Pacaud D, Petryk A, Collett-Solberg PF, Kappy M. Vitamin D Deficiency in Children and Its Management: Review of Current Knowledge and Recommendations. *Pediatrics.* 2008;122:398–417.

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FIELD CORRECTION EFFECTIVENESS CHECK

Vitamin D Total– Change in Correlation Between Serum and Plasma Specimen Tubes

This response form is to confirm receipt of the enclosed Siemens Healthcare Diagnostics Urgent Field Safety Notice CC 16-14.A.OUS dated October, 2016 regarding Vitamin D Total– Change in Correlation Between Serum and Plasma Specimen Tubes.

Please read the question and indicate the appropriate answer.

Fax this completed form to Siemens Healthcare Diagnostics at the fax number provided at the bottom of this page.

1. I have read and understood the Urgent Field Safety Notice instructions provided in this letter. Yes ☐ No ☐

Name of person completing questionnaire:

Title:

Institution: Instrument Serial Number:

Street:

City: State:

Phone: Country:

To fax this completed form please send it to the Customer Care Center at (###) ###-####. If you have any questions, contact your local Siemens technical support representative.

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