VIDAS® 25 OH Vitamin D TOTAL (VITD)

IVD

VIDAS 25 OH Vitamin D TOTAL (VITD) is an automated quantitative test for use on the instruments of the VIDAS family for the determination of 25-hydroxyvitamin D Total in human serum or plasma using the ELFA technique (Enzyme Linked Fluorescent Assay).
The VIDAS 25 OH Vitamin D TOTAL assay is to be used as an aid in the assessment of Vitamin D sufficiency.

SUMMARY AND EXPLANATION

Vitamin D is a fat-soluble steroid prohormone. Vitamin D deficiency can be associated with rickets in children, and osteoporosis and secondary hyper-parathyroidism in adults. Recent studies have established a link between low circulating vitamin D levels and an increasing risk of diabetes, cardiovascular or autoimmune diseases as well as various forms of cancer (1-8). Vitamin D testing has become an assay of general health status (9).
Vitamin D is found mainly in two forms: vitamin D2 (ergocalciferol) and vitamin D3 (cholecalciferol). Vitamin D3 is synthesized from 7-dehydrocholesterol by action of solar ultraviolet radiation on the skin. It is also present in food (mostly in fatty fish). Vitamin D2 is from exogenous origin only. Small amounts of vitamin D2 are present in food (mushrooms, vegetables). Both vitamins D2 and D3 are used for medical supplementation and are identically metabolized by the body.
The active form of the molecule is the 1,25-$(OH)_2$ vitamin D (calcitriol) which is obtained from vitamin D through two successive hydroxylation reactions. The first hydroxylation occurs in the liver to yield 25-(OH) vitamin D (calcidiol). The second hydroxylation occurs in the kidneys and other tissues as well to yield biologically active 1,25-$(OH)_2$ vitamin D. The 25-(OH) vitamin D is the main storage form of vitamin D in the human body. It is found in high concentrations in serum or plasma, which makes 25-(OH) vitamin D the preferred analyte for the determination of vitamin D nutritional status (10).

PRINCIPLE

The assay principle combines an enzyme immunoassay competition method with a final fluorescent detection (ELFA).
The Solid Phase Receptacle (SPR®) serves as the solid phase as well as the pipetting device for the assay. Reagents for the assay are ready-to-use and pre-dispensed in the sealed reagent strips.
All of the assay steps are performed automatically by the instrument. The reaction medium is cycled in and out of the SPR several times.
The sample is mixed with pre-treatment reagent to separate vitamin D from its binding protein.
The pre-treated sample is then collected and transferred into the well that contains an alkaline phosphatase (ALP)-labeled anti-vitamin D antibody (conjugate).
The vitamin D antigen present in the sample and the vitamin D antigen coating the interior of the SPR compete for binding sites on the anti-vitamin D antibody-ALP conjugate.
During the final detection step, the substrate (4-Methyl-umbelliferyl phosphate) is cycled in and out of the SPR. The conjugate enzyme catalyzes the hydrolysis of this substrate into a fluorescent product (4-Methyl-umbelliferone), the fluorescence of which is measured at 450 nm. The intensity of the fluorescence is inversely proportional to the concentration of vitamin D antigen present in the sample. At the end of the assay, results are automatically calculated by the instrument in relation to the calibration curve stored in memory, and then printed out.

KIT COMPOSITION (60 TESTS):

60 VITD Strips	STR	Ready-to-use. Stabilizer of human origin*.
60 VITD SPRs 2 x 30	SPR	Ready-to-use. Interior of SPR coated with vitamin D.
Control VITD 1 x 1.5 mL (liquid)	C1	Ready-to-use. 25-(OH) Vitamin D diluted in human serum* + preservative. MLE data indicate the confidence interval in ng/mL ("Control C1 Dose Value Range").
Calibrator VITD 1 x 2.5 mL (liquid)	S1	Ready-to-use. 25-(OH) Vitamin D diluted in human serum* + preservative. MLE data indicate the calibrator or standard concentration in ng/mL ("Calibrator (S1) Dose Value") and the confidence interval in "Relative Fluorescence Value ("Calibrator (S1) RFV Range).
Specifications for the factory master data required to calibrate the test: • MLE data (Master Lot Entry) provided in the kit, or • MLE bar code printed on the box label.		
1 Package insert provided in the kit or downloadable from www.biomerieux.com/techlib.		

***** This product has been tested and shown to be negative for HBs antigen and antibodies to HIV1, HIV2 and HCV. However, since no existing test method can totally guarantee their absence, this product must be treated as potentially infectious. Therefore, usual safety procedures should be observed when handling.

The SPR

The interior of the SPR® is coated during production with vitamin D. Each SPR is identified by the "VITD" code. Only remove the required number of SPRs from the pouch and **carefully reseal the pouch after opening**.

The Reagent Strip

The strip consists of 10 wells covered with a labeled, foil seal. The label comprises a bar code which mainly indicates the assay code, kit lot number and expiration date. The foil of the first well is perforated to facilitate the introduction of the sample. The last well of each strip is a cuvette in which the fluorometric reading is performed. The wells in the center section of the strip contain the various reagents required for the assay.

Description of the VITD strips:

Wells	Reagents
1	Sample Well.
2	Conjugate: TRIS, NaCl + anti-vitamin D antibody conjugated with alkaline phosphatase + stabilizer of human origin* + preservative (300 µL).
3	Pre-treatment solution: TRIS, NaCl + dissociation agent + surfactant + methanol** (600 µL).
4-5-6	Empty well
7-8-9	Wash buffer: TRIS, NaCl + preservative + surfactant (600 µL).
10	Reading cuvette with substrate: 4-Methyl-umbelliferyl phosphate (0.6 mmol/l) + diethanolamine*** (DEA) (0.62 mol/L or 6.6%, pH 9.2) + 1 g/L sodium azide (300 µL).

***** This product has been tested and shown to be negative for HBs antigen and antibodies to HIV1, HIV2 and HCV. However, since no existing test method can totally guarantee their absence, this product must be treated as potentially infectious. Therefore, usual safety procedures should be observed when handling.

** Signal Word: **ATTENTION**

Hazard statement

H302 + H312 + H332 : Harmful if swallowed, in contact with skin or if inhaled..
H315 : Causes skin irritation.
H319 : Causes serious eye irritation..
H371 : May cause damage to organs.

Precautionary statement

P280 :Wear protective gloves/protective clothing/eye protection/face protection.
P270 : Do not eat, drink or smoke when using this product..
P309 + P311 : IF exposed or if you feel unwell: Call a POISON CENTER or doctor/physician.
P305 + P351 + P338: IF IN EYES: Rinse cautiously with water for several minutes. Remove contact lenses, if present and easy to do. Continue rinsing.

*** Signal Word: **DANGER**

Hazard statement

H318 : Causes serious eye damage.

Precautionary statement

P280 :Wear protective gloves/protective clothing/eye protection/face protection.
P305 + P351 + P338: IF IN EYES: Rinse cautiously with water for several minutes. Remove contact lenses, if present and easy to do. Continue rinsing.

For further information, refer to the Safety Data Sheet.

MATERIALS AND DISPOSABLES REQUIRED BUT NOT PROVIDED

- Pipette with disposable tip to dispense 100 µL.
- Powderless, disposable gloves.
- For other specific materials and disposables, please refer to the Instrument User's Manual.
- Instrument of the VIDAS family.

WARNINGS AND PRECAUTIONS

- **For *in vitro* diagnostic use only.**
- **For professional use only.**
- **This kit contains products of human origin. No known analysis method can totally guarantee the absence of transmissible pathogenic agents. It is therefore recommended that these products be treated as potentially infectious and handled observing the usual safety precautions (see Laboratory biosafety manual - WHO - Geneva - latest edition).**
- This kit contains products of animal origin. Certified knowledge of the origin and/or sanitary state of the animals does not totally guarantee the absence of transmissible pathogenic agents. It is therefore recommended that these products be treated as potentially infectious and handled observing the usual safety precautions (do not ingest or inhale).
- Do not use the SPRs if the pouch is pierced or if the dot sealing a SPR is detached.
- Do not use visibly deteriorated STRs (damaged foil or plastic).
- Do not use reagents after the expiration date indicated on the label.
- Do not mix reagents (or disposables) from different lots.
- **Use powderless gloves**, as powder has been reported to cause false results for certain enzyme immunoassay tests.
- Kit reagents contain sodium azide which can react with lead or copper plumbing to form explosive metal azides. If any liquid containing sodium azide is disposed of in the plumbing system, drains should be flushed with water to avoid build-up.
- The reading cuvette with pre-treatment solution (well 3) contains a harmful reagent (methanol = CH_3OH). Refer to the hazard statements "H" and the precautionary statements "P" above.
- The reading cuvette with substrate (well 10) contains an irritant agent (6.6% diethanolamine). Refer to the hazard statements "H" and the precautionary statements "P" above.
- Spills should be wiped up thoroughly after treatment with liquid detergent or a solution of household bleach containing at least 0.5% sodium hypochlorite. See the User's Manual for cleaning spills on or in the instrument. Do not autoclave solutions containing bleach.
- The instrument should be regularly cleaned and decontaminated (see the User's Manual).

STORAGE CONDITIONS

- Store the VIDAS 25 OH Vitamin D TOTAL kit at 2-8°C.
- **Do not freeze reagents.**
- **Store all unused reagents at 2-8°C.**
- After opening the kit, check that the SPR® pouch is correctly sealed and undamaged. If not, do not use the SPRs.
- **Carefully reseal the pouch with the desiccant inside after use to maintain stability of the SPRs and return the complete kit to 2-8°C.**
- If stored according to the recommended conditions, all components are stable until the expiration date indicated on the label.

SPECIMENS

Specimen type and collection:

Human serum or plasma (lithium heparin).
Do not use EDTA tubes.

Types of tubes validated:

- Plastic tube with clot activator,
- Plastic tube with separation gel and clot activator,
- Plastic tube with lithium heparin,
- Plastic tube with lithium heparin and separation gel.

Note: Blood collection tube results may vary from one manufacturer to another depending on the materials and additives used.
It is the responsibility of each laboratory to validate the type of sample tube used and to follow the manufacturer's recommendations for use.
Samples containing suspended fibrin particles or erythrocyte stroma should be centrifuged before testing.

Specimen preparation

Plain tubes: wait for samples to coagulate and **centrifuge** according to the tube manufacturer's recommendations to eliminate fibrin.

Other tubes: follow the tube manufacturer's recommendations for use.

Frozen-stored samples: after thawing, these samples must be homogenized before testing. Mix using a vortex-type mixer. Clarify the samples before analysis by centrifugation, if necessary.

The pre-analytical step including the preparation of blood samples is an essential first step when performing medical analyses. In conformity with Good Laboratory Practices, this step is the responsibility of the laboratory manager.

Insufficient clot time can result in the formation of fibrin with micro-clots that are invisible to the naked eye. The presence of fibrin, red blood cells, or suspended particles can lead to erroneous results.

Samples containing suspended fibrin particles or erythrocyte stroma should be centrifuged before testing.

For serum specimens, ensure that complete clot formation has taken place prior to centrifugation. Some specimens, especially those from patients receiving anticoagulant or thrombolytic therapy, may exhibit increased clotting times.

Specimen-related interferences

Interferences have been studied according to the recommendations of Clinical and Laboratory Standards Institute (CLSI®) document EP7-A2 (11).

None of the following factors have been found to significantly influence this assay:
- hemolysis (after spiking samples with hemoglobin: 0 to 1.9 g/L (monomer)),
- lipemia (after spiking samples with lipids: 0 to 4.0 g/L equivalent in triglycerides),
- bilirubinemia (after spiking samples with bilirubin: 0 to 0.3 g/L),
- cholesterol (after spiking samples with cholesterol: 0 to 5 g/L).

However, it is recommended not to use samples that are clearly hemolyzed, lipemic or icteric and, if possible, to collect a new sample.

Specimen stability

Serum and plasma samples can be stored in primary tube at 18-25°C for up to 8 hours or aliquoted at 2-8°C for up to 5 days; if longer storage is required, freeze the sera or plasma at–25 ± 6°C. Serum-type samples can be stored for 3 months at -25 ± 6°C, with 3 freeze/thaw cycles. Plasma-type samples can be stored for 3 months at -25 ± 6°C, with 3 freeze/thaw cycles.

INSTRUCTION FOR USE

For complete instructions, see the User's Manual.

Reading VIDAS® Protocole Test Change (PTC) protocol data and MLE data

When using the assay for the first time:

With the external instrument barcode reader,
1. Scan the PTC barcode(s) at the end of the package insert. or downloadable from www.biomerieux.com/techlib. This reading allows VIDAS® PTC protocol data to be transferred to the instrument software for its update.
2. Scan the MLE data on the box label.

Note: If the MLE data have been read before the VIDAS® PTC protocol, read the MLE data again.

When opening a new lot of reagents:

Enter the specifications (or factory master data) into the instrument using the master lot entry (MLE) data.
If this operation is not performed before initiating the tests, the instrument will not be able to print results.
Note: the master lot data need only be entered once for each lot.
It is possible to enter MLE data **manually or automatically** depending on the instrument (refer to the User's Manual).

Calibration

Calibration, using the calibrator provided in the kit, must be performed each time a new lot of reagents is opened, after the master lot data have been entered. Calibration should then be performed every 28 days. This operation provides instrument-specific calibration curves and compensates for possible minor variations in assay signal throughout the shelf-life of the kit.
The calibrator, identified by S1, must be tested **in duplicate** (see User's Manual). The calibrator value must be within the set RFV ("Relative Fluorescence Value"). If this is not the case, recalibrate using S1.

Procedure

1. **Only remove the required reagents from the refrigerator. They can be used immediately.**
2. Use one "VITD" strip and one "VITD" SPR® from the kit for each sample, control or calibrator to be tested. **Make sure the storage pouch has been carefully resealed after the required SPRs have been removed.**
3. The test is identified by the **"VITD"** code on the instrument. The calibrator must be identified by "S1", and tested **in duplicate**. If the control is to be tested, it should be identified by "C1".
4. If necessary, clarify the samples by centrifugation.
5. Mix the calibrator, control and samples using a vortex-type mixer (for serum or plasma separated from the pellet).
6. Before pipetting ensure that samples, calibrators, controls and diluent are free of bubbles.
7. **For this test, the calibrator, control, and sample test portion is 100 µL.**
8. Insert the "VITD" SPRs and "VITD" strips into the instrument. Check to make sure the color labels with the assay code on the SPRs and the Reagent Strips match.
9. Initiate the assay as directed in the User's Manual. All the assay steps are performed automatically by the instrument.
10. Reclose the vials and return them to 2–8°C after pipetting.
11. The assay will be completed **within approximately 40 minutes.** After the assay is completed, remove the SPRs and strips from the instrument.
12. Dispose of the used SPRs and strips into an appropriate recipient.

RESULTS AND INTERPRETATION

Once the assay is completed, results are analyzed automatically by the computer. Fluorescence is measured twice in the Reagent Strip's reading cuvette for each sample tested.
The first reading is a background reading of the substrate cuvette before the SPR is introduced into the substrate. The second reading is taken after incubating the substrate with the enzyme remaining on the interior of the SPR. The RFV (Relative Fluorescence Value) is calculated by subtracting the background reading from the final result. This calculation appears on the result sheet.
The results are automatically calculated using calibration curves which are stored by the instrument (4-parameter logistics model) and are expressed in ng/mL or nmol/L.
Assay results should be used in conjunction with other clinical or laboratory data to assist the clinician in making individual patient management decisions.

QUALITY CONTROL

One control is included in each VIDAS 25 OH Vitamin D TOTAL kit.
This control must be performed immediately after opening a new kit to ensure that reagent performance has not been altered. Each calibration must also be checked using this control. The instrument will only be able to check the control value if it is identified by C1.
Results cannot be validated if the control value deviates from the expected value.

Note

It is the responsibility of the user to perform Quality Control in accordance with any local applicable regulations.

LIMITATIONS OF THE METHOD

- Interference may be encountered with certain sera containing antibodies directed against reagent components. For this reason, assay results should be interpreted taking into consideration the patient's history, and the results of any other tests performed.

RANGE OF EXPECTED VALUES

It is recommended that each laboratory establish its own reference range, which may be unique to the population it serves. A review of the most recent literature suggests the recommendation for 25-OH Vitamin D levels are (12):

Status	25-(OH) vitamin D
Deficient	< 20 ng/ml
Insufficient	20-29 ng/ml
Sufficient	30-100 ng/ml
Potential toxicity	> 100 ng/ml

A reference range study was conducted using 140 apparently healthy adults, based on guidance from CLSI C28-A3. Serum samples were collected in from a French population between January and December, and were tested using VIDAS 25 OH Vitamin D TOTAL assay. The values observed are summarized below*:

Observed values (n=140)	25-(OH) vitamin D (ng/ml)
Median	23.1
Observed range (2.5th to 97.5th percentile)	9.3 – 48.5

(*) Indicative results: the results obtained can vary from one laboratory to another and according to the geographical zones.

PERFORMANCE

Studies performed using VIDAS® 25 OH Vitamin D TOTAL kit gave the following results:

Measurement range

The VIDAS 25 OH Vitamin D TOTAL measurement range extends from 8.1 ng/mL up to 126.0 ng/mL. Values below the lower limit of the measurement range are reported as < 8.1 ng/mL. Values above the upper limit of the measurement range are reported as > 126.0 ng/mL.

Detection and quantitation limits

The Limit of Blank is the 95th percentile of more than 60 measurements of analyte free samples. LoB corresponds to the concentration below which the probability to obtain analyte-free samples is 95%. LoB was determined to be 6.2 ng/mL.

The Limit of Detection (LoD) is the concentration of 25(OH) Vitamin D in a sample that can be distinguished from the analyte free sample with a probability of 95%. The LoD was determined to be 8.1 ng/mL.

The Limit of Quantitation (LoQ) is the lowest concentration of 25(OH) Vitamin D that can be quantified with a level of acceptable accuracy and precision. The LoQ was determined to be 8.1 ng/mL.
The study was performed as recommended by CLSI® document EP17-A2.

Functional detection limit

The functional detection limit is defined as the concentration of 25(OH) Vitamin D measured with an inter-assay coefficient of variation of 20%. During an in-house study, the functional detection limit was determined to be < 8.1 ng/mL.

Linearity

The VIDAS 25 OH Vitamin D TOTAL assay is linear over its measurement range (7.1 à 126.2 ng/mL), evaluated according to the recommendations of CLSI® document EP6-A.

Precision

A study was performed according to the recommendations of CLSI® document EP5-A2. A panel of 5 human samples covering the measurement range was tested as follows: each sample was tested in duplicate in 2 separate runs per day over 20 days, using two reagent lots (10 test days per reagent lot) on 3 instruments (N=240 values per sample). The 3 instruments were located at one site. Two calibrations were used for each reagent lot (5 test days per calibration for each lot). The repeatability (within-run precision) and reproducibility (within-instrument between-lot) were calculated for each sample using this protocol and are reported in the following table:

Sample	N	Mean concentration (ng/mL)	Repeatability		(Within-instrument between-lot) reproducibility	
			Standard deviation (ng/mL)	CV (%)	Standard deviation (ng/mL)	CV (%)
Sample 1	240	17.1	1.1	6.4	1.8	10.5
Sample 2	240	21.6	1.1	5.2	1.7	8.1
Sample 3	240	30.5	1.3	4.2	1.7	5.6
Sample 4	240	46.7	1.4	3.0	2.3	4.9
Sample 5	240	100.0	2.4	2.4	3.3	3.3

Specificity

The specificity of the VIDAS 25 OH Vitamin D TOTAL assay was assessed by testing cross-reactants according to the recommendations of the CLSI® document EP7-A2. Cross-reactivity was evaluated by adding the following substances to samples containing 25(OH) Vitamin D. The results of this study are summarized in the following table:

Tested compound	Concentration	% Cross reactivity[a]
Vitamin D2	100 ng/mL	9
Vitamin D3	100 ng/mL	6
$1,25(OH)_2$ Vitamin D2 *	100 ng/mL	6
$1,25(OH)_2$ Vitamin D3 *	100 ng/mL	81
$24,25(OH)_2$ Vitamin D3 *	10 ng/mL	588
3 epi 25(OH) Vitamin D3	100 ng/mL	5

* levels tested were 10x to 1000x the typical endogenous levels of analyte

a $$\text{Cross reactivity (\%)} = \frac{\text{Mean Value spiked (ng/ml)} - \text{Mean Value unspiked (ng/ml)}}{\text{concentration of cross - reactant (ng/ml)}} \times 100$$

The cross-reactivity **b** to 25(OH) Vitamin D2 was determined using natural sera that contain endogenous 25(OH) Vitamin D, without spiking. Samples were analyzed by liquid chromatography coupled to mass spectrometry method (LC-MS/MS) in order to determine 25(OH) Vitamin D2 and 25(OH) Vitamin D3 respective concentrations. Samples that were included in this study showed a ratio [25(OH) Vitamin D2]/[25(OH) Vitamin D3] >4.

b $$\text{25(OH) Vitamin D2 cross reactivity (\%)} = \frac{\text{25(OH)D (Vidas)} - \text{25(OH)D3 (LC - MS/MS)}}{\text{25(OH)D2 (LC - MS/MS)}} \times 100$$

The mean 25(OH) Vitamin D2 cross reactivity for VIDAS 25 OH Vitamin D TOTAL assay is 91%.

Interference

The VIDAS 25 OH Vitamin D TOTAL was evaluated for interference consistent with CLSI document EP7 A2.

None of the following factors have been found to significantly influence this assay:

Human Albumin	0 to 60 g/L
Rheumatoid factors	0 à 577.7 IU/mL
HAMA	0 à 2 µg/mL

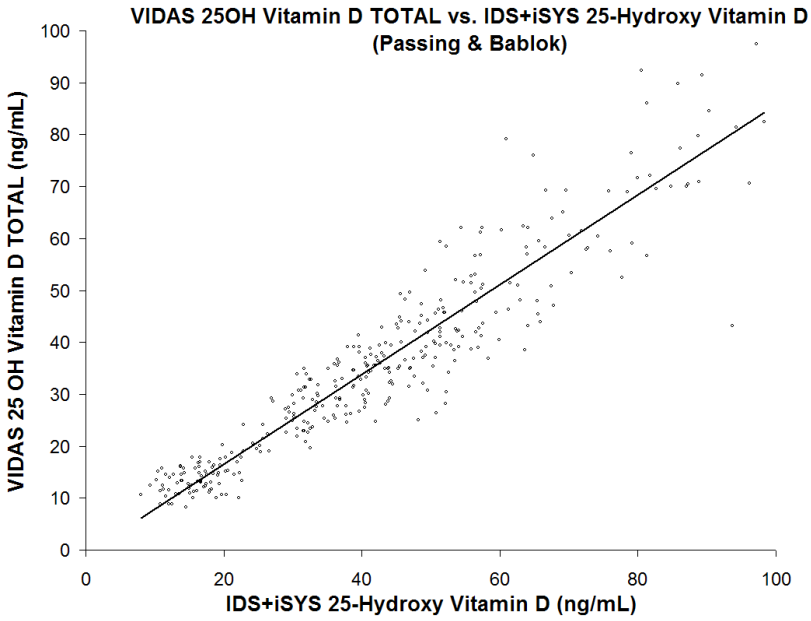
Method comparison

1) A comparison of the VIDAS 25 OH Vitamin D TOTAL assay (Y) with the IDS-iSYS 25-Hydroxy Vitamin D assay (X) assay gave the following results:

Number of samples analyzed: 344

Equation for Passing-Bablok regression: Y = 0.87 X – 0.81

Coefficient of correlation: 0.93



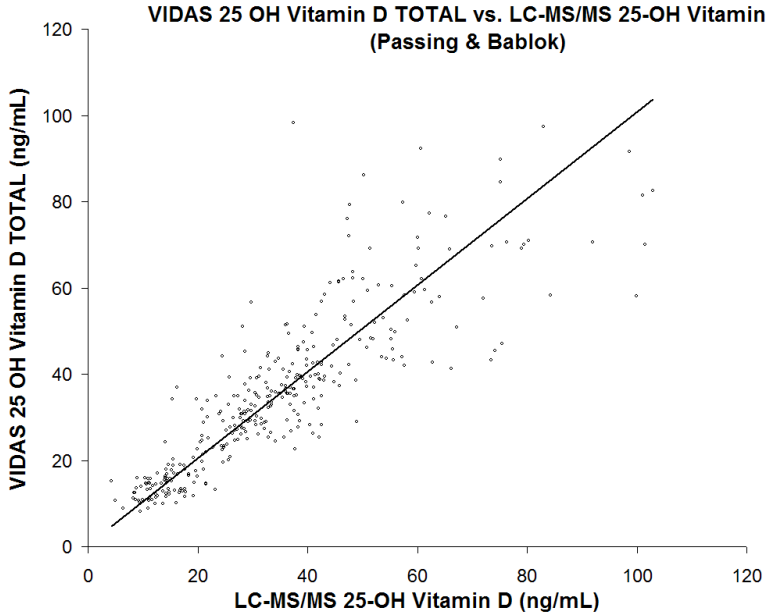
The sample concentrations analyzed with VIDAS 25 OH Vitamin D TOTAL ranged between 8.2 ng/mL and 98.2 ng/mL.

2) A comparison of the VIDAS 25 OH Vitamin D TOTAL assay (Y) with a LC-MS/MS method (X) assay gave the following results:

Number of samples analyzed: 343

Equation for Passing-Bablok regression: Y = 1.00 X + 0.41

Coefficient of correlation: 0.86



The sample concentrations analyzed with VIDAS 25 OH Vitamin D TOTAL ranged between 8.2 ng/mL and 98.2 ng/mL.

WASTE DISPOSAL

Dispose of used or unused reagents as well as any other contaminated disposable materials following procedures for infectious or potentially infectious products.
It is the responsibility of each laboratory to handle waste and effluents produced according to their nature and degree of hazardousness and to treat and dispose of them (or have them treated and disposed of) in accordance with any applicable regulations.

LITERATURE REFERENCES

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INDEX OF SYMBOLS

Symbol	Meaning
REF	Catalog number
IVD	*In Vitro* Diagnostic Medical Device
	Manufacturer
	Temperature limit
	Use by
LOT	Batch code
	Consult Instructions for Use
	Contains sufficient for <n> tests
	Date of manufacture

WARRANTY

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REVISION HISTORY

Change type categories :

N/A	Not applicable (First publication)
Correction	Correction of documentation anomalies
Technical change	Addition, revision and/or removal of information related to the product
Administrative	Implementation of non-technical changes noticeable to the user
Note:	*Minor typographical, grammar, and formatting changes are not included in the revision history.*

Release date	Part Number	Change Type	Change Summary
2015/01	9304004C	Administrative	REVISION HISTORY INDEX OF SYMBOLS
		Technical	KIT COMPOSITION (60 TESTS) WARNINGS AND PRECAUTIONS
2015/06	9304004D	Technical	KIT COMPOSITION (60 TESTS) INSTRUCTIONS FOR USE

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