Comparison of Analytical Validation of Immunoassays and Mass Spectrometry Assays in FDA-Cleared In Vitro Diagnostic Devices

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Disclosures

I have no financial conflicts to disclose

Agenda

1. Overview of the FDA Submission Process

2. Comparison of Analytical Validation Studies for Vitamin D Mass Spectrometry and Immunoassay IVDs

In Vitro Diagnostic (IVDs) Are:

- Reagents, instruments, and systems used in diagnosis of disease or other conditions…
- In order to cure, mitigate, treat, or prevent disease…
- Intended for use in the collection, preparation, and examination of specimens taken from the human body.

[21 CFR 809.3]

Devices Are Evaluated According to Risk

- Class I: low risk (e.g., mass spectrometry instruments)
- Class II: moderate risk (e.g., prostate cancer monitoring)
- Class III: high risk (e.g., screening for colon cancer)

- Each risk class has its own standard of evidence and requirements for review

Device Classification and Review

	Class I	Class II		Class III
Risk	Low	Moderate		High
Clearance/ Approval	Not Required	510(k)	De Novo	PMA
Comparison	Not Required	Predicate Device	Clinical Truth	Clinical Truth
Controls	General	General + Special Controls		
Submission Studies*	Not Required*	Analytical and Clinical		

Marketed **Cleared** **Granted** **Approved**

*Most Class I and some Class II IVDs are “exempt” from pre-market review

Regulatory controls

These are provisions in the regulations that, when followed, ensure that device is safe and effective.

- General Controls: sufficient for most class I devices, examples include:
  - Facility registration (21 CFR 807.20)
  - Device listing (21 CFR 807.20)
  - Labeling requirements (21 CFR 801 or 809)
  - Maintaining records and reporting on recalls and adverse events (21 CFR 806 or 810)
- Special Controls: Special controls are regulatory requirements for class II devices.
  - Mandatory analytical and clinical performance standards
  - Special Labeling Requirements
  - Postmarket surveillance

Regulatory controls guidance document:
https://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/Overview/GeneralandSpecialControls/default.htm

What Does FDA Review in a Submission?

1. Intended Use/Indications for Use
2. Analytical performance testing
3. Clinical performance testing
4. Device labeling (package insert/instructions for use)

Intended Use/Indications for Use

1. Determines risk of device and performance testing required

2. What the device is:

   A. Analyte that is measured
   B. The measurement principle of the test
   C. The specimen type

3. The context in which the device is used:

   A. The setting (clinical laboratory, point-of-care, etc.)
   B. Instrumentation required
   C. The target condition
   D. The clinical purpose (diagnosis, prognosis, monitoring)
   E. The target population for whom the test is intended

Analytical Performance Testing

- Precision
- Linearity/assay reportable range
- Detection Limit/Analytical Sensitivity
- Cross reactivity/ Interfering substances
- Method comparison (to the predicate or reference method)
- Matrix comparison
- Traceability, Stability, Expected values
- Controls and calibrators

CDRH-Recognizes Guidelines for IVDs

Clinical and Laboratory Standards Institute (CLSI)

Precision

Liquid Chromatography-Mass Spectrometry Methods

Analytical Sensitivity

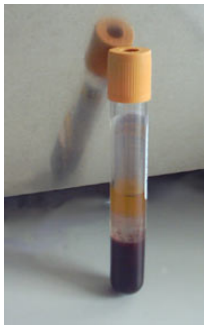
AND MANY MORE!

http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfStandards/search.cfm

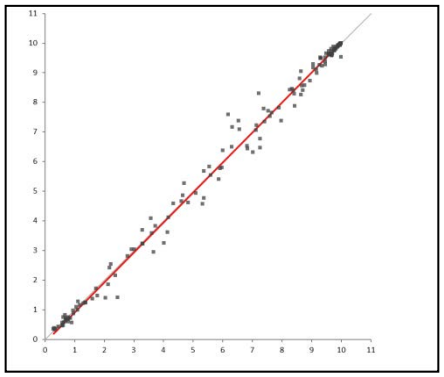
Use of CDRH-recognized guidelines can make performance testing and submission review faster and more efficient

General Recommendations for Analytical Performance Testing

Use Recognized CLSI Guidelines

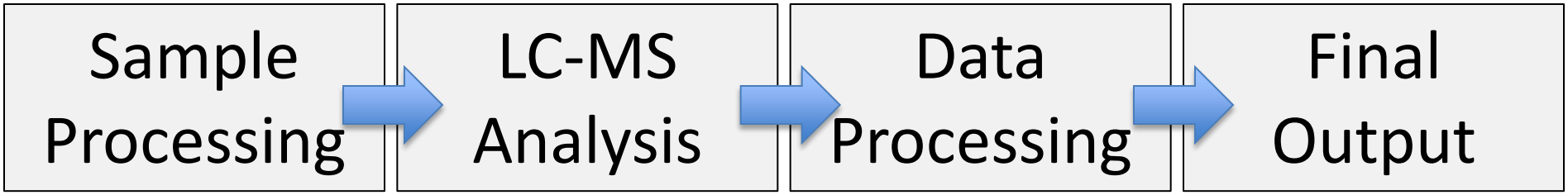


Use Real Patient Samples from the Intended Use Population and Intended Matrix



Test Samples that Cover the Analytical Measuring Range and at Medical Decision Points

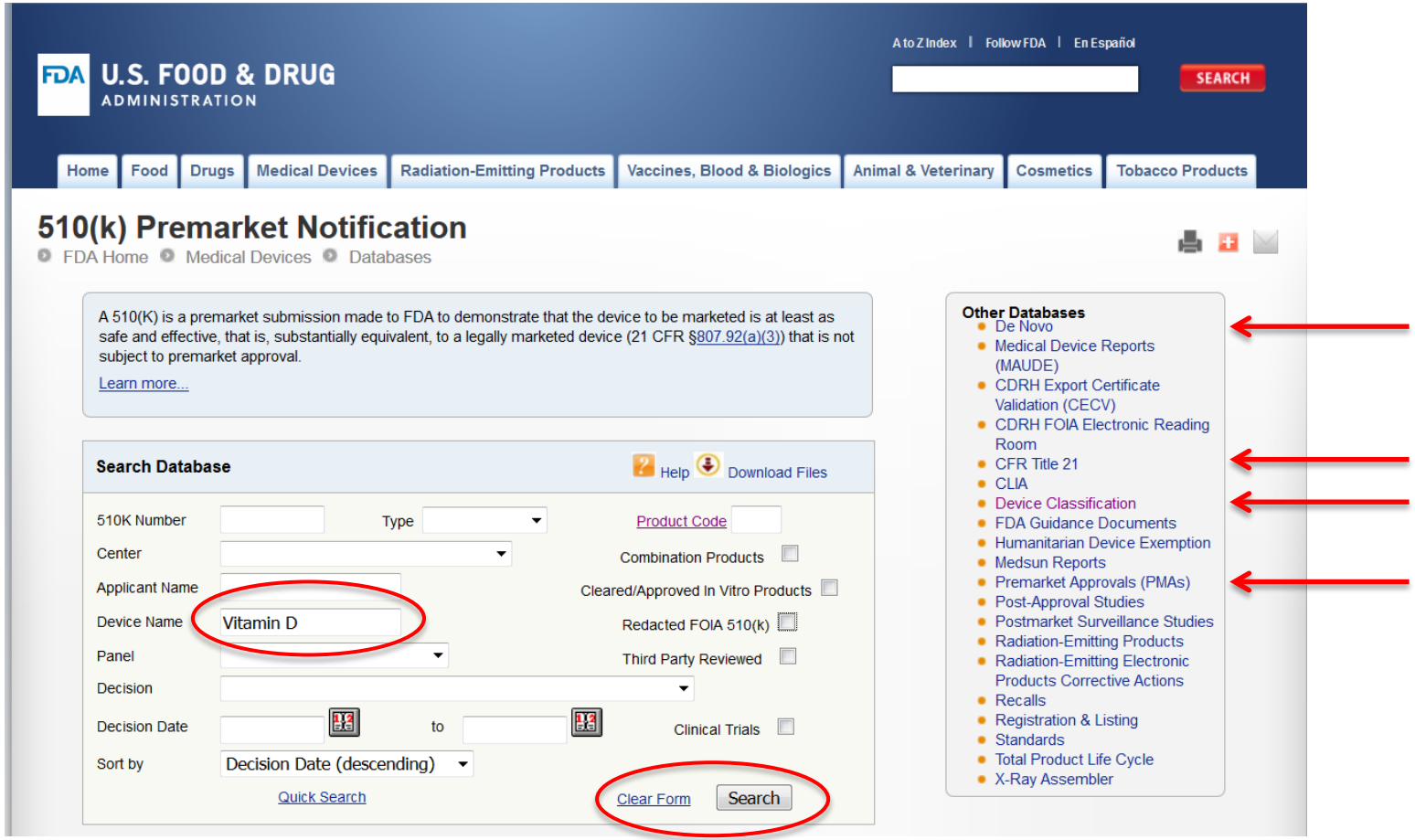
Use the Final Finished Device for All Performance Testing



Where to Find Information on Analytical Testing Performed for Cleared Devices

The 510k database

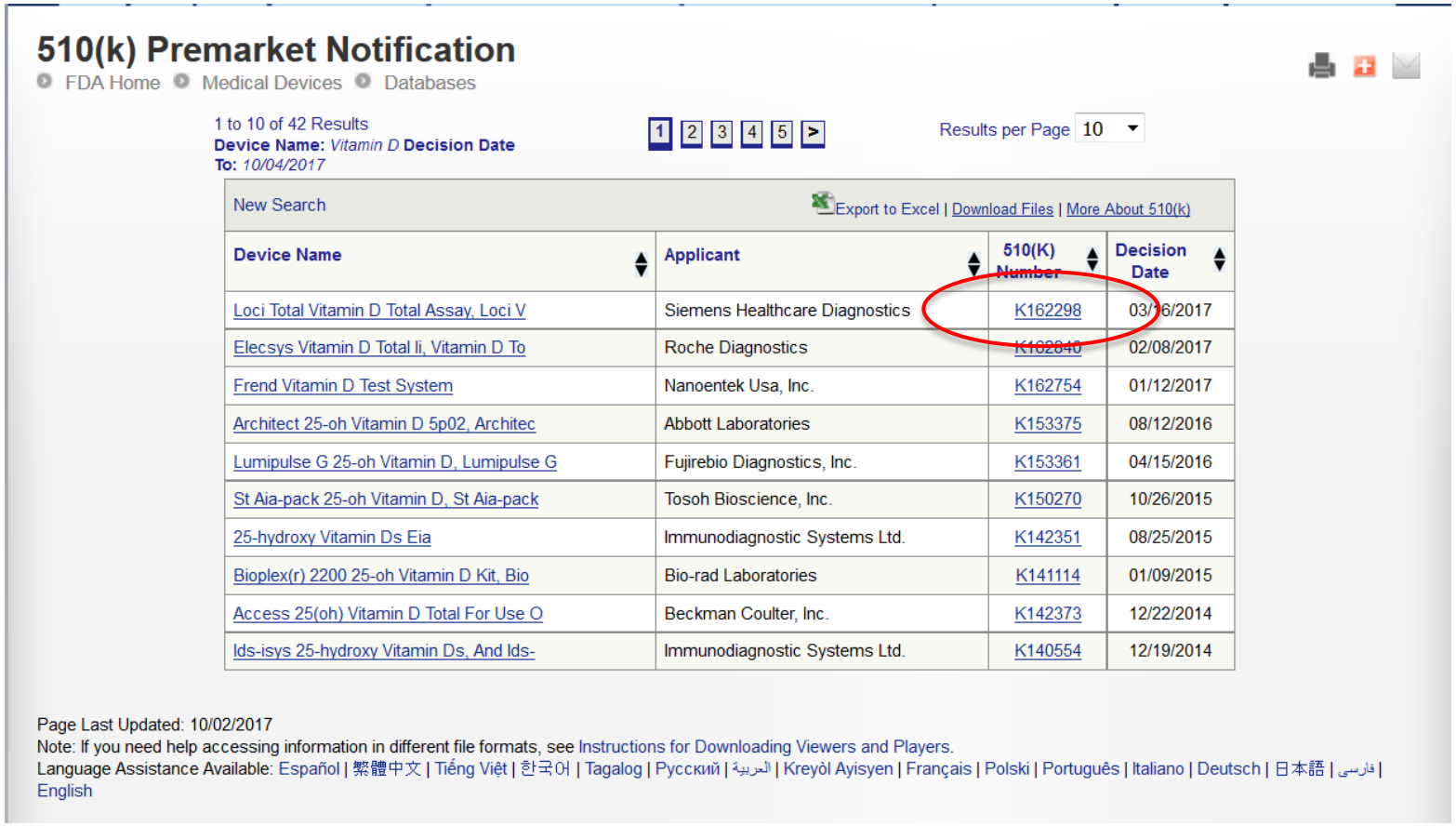
https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpmn/pmn.cfm



Where to Find Information on Analytical Testing Performed for Cleared Devices

The De Novo database

510(k)s for IVDs That Measure Vitamin D



510(k) Premarket Notification

FDA Home ⊙ Medical Devices ⊙ Databases

1 to 10 of 42 Results
Device Name: *Vitamin D* **Decision Date**
To: *10/04/2017*

1 2 3 4 5 >

Results per Page 10

New Search | Export to Excel | Download Files | More About 510(k)

Device Name	Applicant	510(K) Number	Decision Date
Loci Total Vitamin D Total Assay, Loci V	Siemens Healthcare Diagnostics	K162298	03/16/2017
Elecsys Vitamin D Total Ii, Vitamin D To	Roche Diagnostics	K162840	02/08/2017
Frend Vitamin D Test System	Nanoentek Usa, Inc.	K162754	01/12/2017
Architect 25-oh Vitamin D 5p02, Architec	Abbott Laboratories	K153375	08/12/2016
Lumipulse G 25-oh Vitamin D, Lumipulse G	Fujirebio Diagnostics, Inc.	K153361	04/15/2016
St Aia-pack 25-oh Vitamin D, St Aia-pack	Tosoh Bioscience, Inc.	K150270	10/26/2015
25-hydroxy Vitamin Ds Eia	Immunodiagnostic Systems Ltd.	K142351	08/25/2015
Bioplex(r) 2200 25-oh Vitamin D Kit, Bio	Bio-rad Laboratories	K141114	01/09/2015
Access 25(oh) Vitamin D Total For Use O	Beckman Coulter, Inc.	K142373	12/22/2014
Ids-isys 25-hydroxy Vitamin Ds, And Ids-	Immunodiagnostic Systems Ltd.	K140554	12/19/2014

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The First LC-MS Device for Vitamin D Granted by FDA

New Search | Back To Search Results

Device Classification Name	25-oh-vitamin D Mass Spectrometry Test System
De Novo Number	DEN170019
Device Name	Vitamin D 200M Assay For The Topaz System
Requester	AB SCIEX LLC 500 Old Connecticut Path Framingham, MA 01701
Contact	Shilpa Sharma
Regulation Number	862.1840
Classification Product Code	PSL
Date Received	03/20/2017
Decision Date	05/18/2017
Decision	Granted (DENG)
Classification Advisory Committee	Clinical Chemistry
Review Advisory Committee	Clinical Chemistry
Reclassification Order	Reclassification Order
FDA Review	Decision Summary
Type	Post-NSE

The First Page of the Decision Summary

DEN170019 (LC-MS)

EVALUATION OF AUTOMATIC CLASS III DESIGNATION FOR
Vitamin D 200M Assay

DECISION SUMMARY

A. DEN Number:

DEN170019

B. Purpose for Submission:

De Novo request for evaluation of automatic class III designation for the Vitamin D 200M Assay for the Topaz System

C. Measurand:

Total 25-hydroxyvitamin D

D. Type of Test:

Liquid Chromatography Tandem Mass Spectrometry (LC-MS/MS)

E. Applicant:

AB SCIEX

F. Proprietary and Established Names:

Vitamin D 200M Assay

K162298 (Immunoassay)

510(k) SUBSTANTIAL EQUIVALENCE DETERMINATION
DECISION SUMMARY
ASSAY ONLY TEMPLATE

A. 510(k) Number:

k162298

B. Purpose for Submission:

New Device

C. Measurand:

25-hydroxyvitamin D

D. Type of Test:

Quantitative chemiluminescent immunoassay

E. Applicant:

Siemens Healthcare Diagnostics

F. Proprietary and Established Names:

LOCI Vitamin D Total Assay

LOCI VITD CAL

Intended Use/Indications for Use

DEN170019 (LC-MS)

The Vitamin D 200M Assay for the Topaz System is intended for in vitro diagnostic use in the **quantitative determination of total 25-hydroxyvitamin D** (25-OH-D) through the measurement of 25-hydroxyvitamin D3 (25-OH-D3) and 25-hydroxyvitamin D2 (25-OH-D2) in **human serum using LC-MS/MS technology** by a trained laboratory professional in a clinical laboratory. **The Assay is intended for use with the Topaz System.** The Vitamin D 200M Assay for the Topaz System is intended to be used in conjunction with other clinical or laboratory data to assist the clinician in making individual patient management decisions in an **adult population** in the **assessment of vitamin D sufficiency.**

K162298 (Immunoassay)

The LOCI Vitamin D Total Assay is an in vitro diagnostic test for the **quantitative measurement of total 25-hydroxyvitamin D** (25-OH-D) **in human serum and plasma** on the **Dimension® EXL™integrated chemistry system** with LOCI® Module. Measurements of vitamin D are used in the **assessment of vitamin D sufficiency.**

Precision (CLSI EP05-A3)

DEN170019 (LC-MS)

Sample	Mean (ng/mL)	Repeatability		Within-Laboratory		Reproducibility	
		SD	%CV	SD	%CV	SD	%CV
1	14.9	0.57	3.8%	1.05	7.0%	1.10	7.3%
2	13.7	0.65	4.7%	0.80	5.8%	0.80	5.8%
3	31.0	1.28	4.1%	2.03	6.5%	2.03	6.5%
4	67.5	3.58	5.3%	3.99	5.9%	5.85	8.7%
5	100	6.37	6.3%	6.46	6.4%	10.4	10.4%
Native Patient Sample	28.4	1.44	5.1%	2.04	7.2%	2.10	7.4%

K162298 (Immunoassay)

Samples	N	Mean	Repeatability		Within-Lab Precision	
		ng/mL	SD	%CV	SD	%CV
QC (Low)	80	18.9	0.58	3.1	1.01	5.4
QC (Level 1)	80	38.7	1.02	2.6	2.02	5.2
QC (Level 2)	80	89.6	1.72	1.9	3.67	4.1
Serum 1	80	8.2	0.46	5.6	0.71	8.7
Serum 2	80	29.4	0.76	2.6	1.46	5.0
Serum 3	80	76.5	1.63	2.1	3.11	4.1
Plasma	80	25.2	0.44	1.8	0.78	3.1

Linearity (CLSI EP06-A)

DEN170019 (LC-MS)

A serum sample with a high concentration of vitamin D was serially diluted with a low concentration serum sample to generate nine samples with vitamin D concentration values of 3.4, 47.7, 91.9, 136, 180, 225, 269, 313, 357 ng/mL, respectively.

The results of the linear regression analyses are summarized below:

$y = 0.9974x + 1.1737$ $R^2 = 0.998$

K162298 (Immunoassay)

A serum sample with a high concentration of vitamin D was serially diluted with a low concentration serum sample to generate nine samples with vitamin D concentration values of 4.4, 24.7, 44.9, 65.1, 85.4, 105.6, 125.8, 146.1 and 163.3 ng/mL respectively.

The results of the linear regression analyses are summarized below:

$y = 1.0222x + 1.3862$, $R^2 = 0.998$

Traceability

DEN170019 (LC-MS)

The assigned 25-hydroxyvitamin D of the Vitamin D 200M Assay for the Topaz System is certified with the CDC Vitamin D Standardization-Certification Program (VDSCP)

K162298 (Immunoassay)

The assay is standardized through the Vitamin D Standardization Program (VDSP).

Analytical Sensitivity (CLSI EP17-A2)

DEN170019 (LC-MS)

LoQ/LLMI Only

The lower limit of the measuring interval (LLMI) for each lot was determined to be the lowest concentration of analyte that achieved both the **bias and precision goals (<20% bias and <20% CV)**

K162298 (Immunoassay)

LoB, LoD, and LoQ

The Limit of Blank (LoB), Limit of Detection (LoD) and Limit of Quantitation (LoQ) studies were performed according to the CLSI EP-17-A2 guideline

LoQ was determined to be 5.0 ng/mL based on **total precision (≤20%)** using all measurements observed on the low serum samples

Analytical Specificity/Interference Testing/Cross-Reactivity (CLSI EP07-A2)

DEN170019 (LC-MS)

The design of the analytical specificity study was based on CLSI EP07-A2 guideline.

K162298 (Immunoassay)

Interference testing was performed according to CLSI EP07-A2

Similar endogenous and exogenous interferents and cross-reactants were tested for both devices, including Vitamin D metabolites.

More interferents were tested in the LC-MS assay to demonstrate that non-Vitamin D metabolites with similar m/z did not interfere with the output of the device

Method Comparison (CLSI EP09-A3)

(This is different for LC-MS vs Immunoassay for Vitamin D)

DEN170019 (LC-MS)

The sponsor performed an accuracy study to the CDC Vitamin D Standardization-Certification Program (VDSCP).

	Passing-Bablok regression results
n	118
Slope	1.008
Intercept	-0.3949
Correlation Coefficient	0.991
Range (ng/mL)	5.6 – 133 ng/mL

From the Special Controls for DEN170019:

"The device must have initial and annual standardization verification by a certifying vitamin D standardization organization deemed acceptable by FDA."

K162298 (Immunoassay)

A method comparison study was performed in accordance to CLSI EP09-A3 to evaluate the accuracy between LOCI Vitamin D Total Assay on the Dimension EXL with LOCI® Module system against the reference method procedure (RMP), University of Ghent's ID-LC-MS/MS. The results were analyzed by standard Passing Bablok regression

n	Sample Range (ng/mL)	Slope (95%CI)	Intercept (95%CI)	r-Value
163	5.2 - 126.1	1.06 (1.01 to 1.12)	0.4 (-0.54 to1.42)	0.977

Summary

1. FDA has regulatory authority to review IVDs before they are marketed in the U.S.
2. I gave an overview of the regulatory process for FDA review of IVDs
3. Analytical performance testing for most analytical studies in Vitamin D submissions are the same for LC-MS and immunoassay IVDs
   A. Interference testing for LC-MS included unrelated metabolites with similar m/z to the Vitamin D analyte
   B. LC-MS IVDs must have initial and annual standardization verification by a certifying vitamin D standardization organization deemed acceptable by FDA

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