FDA Overview of the Process for Clearance and Approval of Mass Spectrometry-based In vitro Diagnostic Devices

MSACL
January 23rd, 2018

Doug Jeffery, Majda Haznadar, Matt Humbard

doug.jeffery@fda.hhs.gov
majda.haznadar@fda.hhs.gov
matthew.humbard@fda.hhs.gov
Disclaimer

This presentation is intended for informational purposes only and does not constitute legal or regulatory advice. Please see the Federal Food, Drug, and Cosmetic Act and 21 CFR Subchapter H for a full list of requirements by FDA.
Disclosures

We have no financial conflicts to disclose
Talk One: Overview (Doug)

1. Goals of this Short Course
2. FDA Organizational Structure
3. Primer on In Vitro Diagnostics (IVDs)
4. How Submissions are Reviewed

• Talk Two: Pre-Submissions (Majda)
• Talk Three: Investigational Device Exemptions (Matt)
• Talk Four: 510(k)s, De Novos, and the Sciex Vitamin D 200M Assay for the Topaz System (Matt)
Goals of This Short Course

1. Have fun!
2. Be interactive!
3. Introduce ourselves
4. Tell you about the role FDA plays in providing essential diagnostic medical devices to patients in the U.S.
OIR Organizational Structure

- DPOM: Policy and Operations
- DRH: Radiological Health Review Divisions
- DMQS: Radiological Health Review Divisions
- DCTD
- DIHD
- DMD
- DMGP

IVD Review Divisions
- Division of Chemistry and Toxicology Devices (Glucose meters, clinical chemistry tests)
- Division of Immunology and Hematology Devices (Hematology analyzers, autoimmune, neurology, flow cytometry)
- Division of Microbiology Devices (infectious diseases, MALDI microorganism Identification)
- Division of Molecular Genetics and Pathology (most cancers, companion diagnostics, NGS)

There are ~300 Employees in OIR Today
In Vitro Diagnostic (IVDs) Are Medical Devices [21 CFR 809.3]:

• 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.
Medical 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
### Some IVD Submission Types

<table>
<thead>
<tr>
<th></th>
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<th>Class III</th>
</tr>
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<td>Clearance/Approval</td>
<td>Not Required*</td>
<td>510(k)</td>
<td>De Novo</td>
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<td></td>
<td></td>
<td>PMA</td>
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<tr>
<td>Pre-Submission</td>
<td>A free submission that allows Device Developers to get early feedback on their design and validation</td>
<td></td>
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<tr>
<td>Investigational Device Exemption</td>
<td>A submission required for some devices that are being used in clinical trials</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Humanitarian Device Exemption</td>
<td>A submission for a device that is intended to treat or diagnose a disease or condition that affects “not more than 8,000” individuals in the U.S.</td>
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</tbody>
</table>

*Most Class I and some Class II IVDs are exempt from pre-market review*
What Does FDA Review in a Submission?

1. Intended Use/Indications for Use
2. Analytical performance testing
3. Clinical performance testing
4. Software
5. Device labeling (package insert/instructions for use)
Submissions Are Reviewed by a Large Team of Experts

Submission Sponsor (IVD Manufacturer)

Review Team
1. Lead Reviewer
2. Consultants: Technical, Analytical, Medical, Statistical
3. Division Management

Administrative Processing
1. Receipt of Electronic Documents
2. Tracking of Deadlines
3. Electronic Sign-in and Sign-out

Clearance or Approval
OVERVIEW OF THE PRE-SUBMISSION PROCESS AT FDA

Majda Haznadar, PhD
Office of In Vitro Devices and Radiological Health
Division of Immunology and Hematology Devices
Immunology and Flow Cytometry Branch
Why Submit a Pre-Submission?

A pre-submission is a way to interact with us early and to shape your pre-market device submission in a way that facilitates clearance or approval.
Features of a Pre-Sub

• Voluntary interaction with the FDA

• It is free!

• Solicit comments and feedback on features of upcoming submissions, such as study design, intended use, statistical analysis approaches and regulatory path

• Always best to get FDA’s current thinking on the clinical and analytical study design
Intended Use/Indications for Use (IU)

• The most important part of any pre-sub

• May be amended/modified over time

• Analytical and clinical validation studies should support the IU of the proposed device

• Clinical study should be conducted in the IU population
IU Elements

- Assay name
- Technology
- Instrument name
- Sample matrices (serum, plasma)
- Quantitative or qualitative
- Clinical use – disease /condition
- The clinical purpose (diagnosis, prognosis, monitoring)
- The target population for whom the test is intended
- Setting (clinical laboratory, point-of-care, etc.)
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.
Analytical Performance Characteristics

- Precision
- Linearity/assay reportable range
- Limit of Detection
- Cross reactivity/ Interfering substances
- Method comparison (to the predicate or reference method)
- Matrix comparison
- Traceability, Stability
- Controls and calibrators
- Reference range (in normal population)
Clinical Performance

• Sensitivity/Specificity, Negative Predictive Value (NPV)/Positive Predictive Value (PPV) based on comparison to a gold standard (i.e., American College of Rheumatology (ACR) classification criteria, biopsy, etc.)

• Specimens: where possible, FDA recommends the set of subjects and specimens to be tested include:

  ➢ Specimens across the entire range of disease state

  ➢ Differential diagnosis specimens (normal samples are not appropriate for determining specificity)
However, a Pre-Submissions is not:

• A pre-review of data

• An appeal regarding a decision on a premarket submission

• A request for classification
Pre-submissions are intended to reduce regulatory uncertainty and can be useful at different stages of device development.
Pre-Submission Content Pointers

• Provide a detailed device description that FDA staff can use to provide useful feedback.
  
  – The more complete the better (does not have to be final device in pre-submission)
  
  – Include study protocols (analytical, clinical, statistical) if you have developed them
  
  – Do not include data
Pre-Sub Example Questions

In general, the more specific that pre-sub questions are, the more helpful will the FDA feedback be. Pre-sub questions can narrow your uncertainty.

Examples of specific pre-sub questions:

Regulatory Strategy:
• Is this an appropriate predicate and therefore the 510(k) is the appropriate path?

Analytical Studies:
• Does FDA agree with the proposal for use of contrived samples in analytical studies described in Section X?
• What happens if my instrument has not been listed for IVD use?

Clinical Studies:
• As described, the clinical study will recruit patients at multiple sites in the EU and the US. Are the EU sites for this study acceptable?

Example of a broad pre-sub question:
• Do the contents of my pre-sub support a 510(k) application?
Pre-Submission Review Process

• DCC directs the submission to appropriate Division/Branch, Branch assigns the submission to Lead Reviewer (LR), your primary point of contact

• LR assembles team- complexity depends on submission:
  ▪ Q14XXXX: LR, Branch chief, Medical Officer
  ▪ Q16XXXX: LR, BC, Deputy Division Director, Division Director, 3 statisticians, 2 Subject Matter Expert (SME) from home division, 1 SME from other Office in OIR, 2 SME from other Centers, 2 medical officers from different Divisions

• LR directs Team reviews, meets, develops answers, provides feedback to sponsors, sets up and runs meeting
Pre-Submission Feedback

• Pre-subs are designed to provide recommendations from the FDA review team.

• Three feedback options; the choice is up to the Sponsor:
  • Email only - written feedback; no response is required. If clarification needed, further supplements can be submitted.
  • Teleconference - written feedback provided at least 5 days prior to call + teleconference with FDA team
  • Face to face - written feedback provided at least 5 days prior to meeting + face to face meeting at White Oak with FDA team

NOTE: Sponsors can, if they like, cancel the meetings if they are satisfied with the written feedback or need more time to review the written feedback.
Pre-Sub Meeting Day

• Meeting slides should be provided electronically at least two business days before the scheduled meeting

• Meeting duration one hour; No audio or video taping is permitted

• After meeting/teleconference held:
  – Sponsor provides draft minutes to DCC within 15 days of meeting
  – FDA reviews/edits minutes within 30 days

• Foreign Visitors need to fill out forms for pre-screening: lack of US citizenship, green card, or US driver’s license at least five days in advance.

  [Link](http://inside.fda.gov:9003/policyprocedures/sopsbyprogram/devicesradiologicalhealth/ucm474294.htm)
How to Submit a Pre-Submission

• Two copies are required (One copy must be an electronic copy (eCopy*))

• Requests are submitted through the Document Control Center (DCC)

• Address for Q-Subs:
  U.S. Food and Drug Administration
  Center for Devices and Radiological Health
  Document Control Center (DCC) WO66-G609
  10903 New Hampshire Avenue Silver Spring, MD 20993-0002

• Q-Sub applicants will receive an acknowledgement letter that contains the Q number

Summary

• Pre-submission are a mechanism for opening up discussions with FDA prior to initiating validation studies.

• I’ve described information that should be contained in your pre-sub.

• Our response is dependent upon the information provided by you.

• Talk to us early!
References

• Guidance Documents:

https://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/default.htm

• Division of Industry and Consumer Education (DICE):

https://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/ContactDivisionofIndustryandConsumerEducation/default.htm

• Device Advice: Comprehensive Regulatory Assistance

https://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/
Thank you!

Questions ?
Investigational Device Exemptions

Devices used in clinical trails
Investigational Device Exemptions

What is an Investigational Device Exemption (IDE)?

An investigational device exemption (IDE) allows the investigational device to be used in a clinical study in order to collect safety and effectiveness data.
Investigational Device Exemption

All clinical evaluations of investigational devices, unless exempt, must have an approved IDE before the study is initiated.

- an investigational plan approved by an institutional review board (IRB). If the study involves a significant risk device, the IDE must also be approved by FDA;
- informed consent from all patients;
- labeling stating that the device is for investigational use only;
- monitoring of the study and;
- required records and reports.
Approved IDE

An approved IDE permits a device to be shipped lawfully for the purpose of conducting investigations of the device without complying with other requirements of the Food, Drug, and Cosmetic Act (FD&C Act) that would apply to devices in commercial distribution.

• You Do Not Need a 510(k) or PMA for an IDE device
• You Do Not have to be registered or list the device with the FDA to obtain an IDE
• Devices under an IDE are exempt from the Quality System (QS) Regulation except for the requirements for design controls (21 CFR 820.30).
Why do I need an IDE?

Does the clearance or approval of your device require you test the device on humans before the clearance? If yes, then you need to know if the use of your device in the clinical trial poses a

- Significant Risk
- Non-significant Risk
Risk analysis of a clinical study
Benefits Vs. Risks

**Benefits**
- Type of benefit
- Magnitude of benefit
- Likelihood of patients experiencing one or more benefits
- Patient perspective on benefit
- Duration of effects
- Benefit factors for healthcare professionals or caregivers
- Medical necessity

**Risks**
- Severity of harm
- Likelihood of risk
- Distribution of nonconforming devices
- Duration of exposure to population
- False-positive or false-negative results
- Patient tolerance on risk
- Risk factors for healthcare professionals or caregivers

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www.fda.gov
How do you know if the study is NSR or SR?

Study Risk Determination Pre-submission

• During a study risk determination presubmission, the FDA will look at your protocol, informed consent, study population, and other factors and determine if you need a FULL IDE application or if your study is exempt from the IDE requirements.
Outcome of a Study Risk Determination Pre-submission

• NSR – non-significant risk
  – You still need IRB approval before study can commence
  – Do not require and IDE submission
  – Needs to be labeled as investigations
  – Informed consent (will be reviewed by the IRB)
  – Records and monitoring (will be reviewed by the IRB)

The IRB may over-rule the NSR determination, in that event, the manufacturer is required to come back to the FDA for an IDE.
Outcome of a Study Risk Determination Pre-submission

• **Significant Risk**
  – You must submit an IDE to the FDA for approval to use the device in the clinical trial.
  – Labeling requirements
  – Distribution limitations
  – Informed consent (reviewed by FDA and IRB)
  – Monitoring (reviewed by FDA)
  – Records and Reporting (both FDA and IRB)
IDEs for New Devices

IDEs for New Indications

Amendments Supplements To IDEs

Diagnostic & Therapeutic IDEs
(21 CFR 812)
Investigational Device Exemption

An example: A pharmaceutical company comes to you, mass spectrometry manufacturer or lab, with a problem. They have a brand new drug that cures a fear of spiders!!!!

It’s going to make everyone rich. The problem is, at plasma concentrations above 100 ng/mL, it destroys your kidneys and there are phenotypical variations in the normal populations that affect the rate of metabolism of the drug.
Investigational Device Exemptions

The drug company needs two things:

1. They need a genetic test to sort the people into the proper groups (fast or slow metabolizers)
2. They need a mass spec device and protocol to monitor plasma concentrations of the spider fear drug during the trial to protect everyone’s kidneys.

BOTH of these devices need an IDE.
Diagnostic & Therapeutic IDEs (21 CFR 812)

- IDEs for New Devices
- IDEs for New Indications
- Amendments Supplements To IDEs

www.fda.gov
IDE for new indications

If you change your intended use of a device, that’s a new device and may need an IDE to conduct the clinical study.

FOR EXAMPLE: adding a new patient population. Addition of neonates to the intended use population can trigger an IDE submission. Should at least trigger a SRD pre-submission.
Investigational Device Exemptions

In Summary,

IDEs are a mechanism to gather clinical data on the safety and effectiveness of a medical device before approval or clearance of the device.

IDEs are required for significant risk studies, which is determined in a study risk determination pre-submission.
510(k)s (and De novos)
Outline

1. Medical Device Classification
2. Intro to 510(k)
3. Overview of MDUFA III Review Process
4. 510(k) Resources
5. 510(k) Today and Tips to a Successful Submission
Medical Device Classification
# Device Classification and Review

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<td><strong>Comparison</strong></td>
<td>Not Required</td>
<td>Predicate Device</td>
<td>Clinical Truth</td>
</tr>
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<td></td>
<td></td>
<td></td>
<td>Clinical Truth</td>
</tr>
<tr>
<td><strong>Controls</strong></td>
<td>General</td>
<td>General + Special Controls</td>
<td></td>
</tr>
<tr>
<td><strong>Submission Studies</strong>*</td>
<td>Not Required*</td>
<td>Analytical and Clinical</td>
<td></td>
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</table>

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

Yes

Sufficient info for special controls?

Yes

Life supporting/sustaining/substantially important to human health?

Yes

Potential unreasonable risk?

Yes

Class I

No

No

Class II

Yes

No

Class III

No

No

Class I

No

No
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](https://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/Overview/GeneralandSpecialControls/default.htm)
EXAMPLES OF CLASS I, II, III DEVICES HERE

Class I: Low Risk - Clinical Chemistry Analyzers, Testosterone (reserved)

Class II: Moderate Risk Tests - potassium, TSH, rheumatoid factor, bilirubin.

Class III: High Risk Tests – PSA, Continuous glucose monitoring systems, fetal fibronectin
Intro to 510(k) – Premarket Notification
What is a 510(k)?

• Demonstration of Substantial Equivalence (SE) to legally marketed device in U.S. also known as a predicate

• For Class II and Class I (reserved) devices.
510(k)’s Intent

There are two outcomes to a 510(k) application:

• Substantially equivalent (SE) to a predicate
• Not Substantially equivalent, automatically into class III
  – PMA – approval of Class III devices
  – de novo
510(k) Remains the Principle Pathway to Obtain Market Authorization for Most Devices

• The 510(k) program was established more than 40 years ago
  – CDRH receives ~3000 510(k)s per year
  – ~90% are found SE and go to market

• Premarket Notification (510(k)) procedures are found in 21 CFR Part 807, Subpart E
  – When a submission is required
  – Exemptions from notification
  – Format and content of the submission
  – Content and format of a 510(k) summary or statement
  – Confidentiality of information
A Device Must be Compared to...

- A legally marketed device (a predicate) that does not require a PMA, i.e.
  - A pre-amendment device (a device used as an IVD prior to 1976)
  - A device found by FDA to be Substantially Equivalent (SE)
  - A reclassified device
  - A device classified by a de novo petition
  - “Paper predicates” can be used

*21 CFR 807.92(a)(3)*
A Paper Predicate

- A paper predicate is a device that only satisfies the LEGAL REGULATORY requirement that you are classified based on the classification of a device you are substantially equivalent to.
- You DO NOT have to compare performance of your device with the paper predicate.
- It is your responsibility to establish the ACCURACY of your device, this is usually done through a method comparison with the predicate.
- You measure “TRUTH” through a reference method or through clinical diagnosis/truth.
- Nearly all submissions have a method comparison to a predicate device.
- For example, DOA immunoassays use GC-MS as their comparator. Troponin assays used clinical diagnosis for AMI.
A 510(k) is appropriate for...

- Introducing device to U.S. market for the first time
- Changing a device’s intended use and/or labeling
- Making modification(s) to device that could affect safety or effectiveness

http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/PremarketSubmissions/PremarketNotification510k/default.htm#whennot
Or Not To Be ....

A 510(k) is NOT required for:

- Private Label Distributer
  - who does not modify device or labeling
  - only adds company name or language like “distributed by__”
- Re-packager or Re-labeler who does not alter the labeling
- Not selling device in US
- Manufacturer of parts
- Devices Exempt by Statute or Regulation – there are currently 1003 class II devices exempt from 510(k) regulations. Calibrators and controls, recently exempt.
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
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.
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)

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

AND MANY MORE!
http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfStandards/search.cfm

Precision

Liquid Chromatography-Mass Spectrometry Methods

Analytical Sensitivity
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

Sample Processing → LC-MS Analysis → Data Processing → Final Output
510(k) Today and Tips to a Successful Submission
510(k) Today

• 510(k) is the largest premarket program at FDA, addressing a great diversity of device types
• There are more than 3,000 510(k) submissions per year, compared to ~100 original PMA applications
• Many significant-risk devices go to market via 510(k) route
• Most 510(k)s are Class II devices (a few are Class I reserved, Testosterone).
Tips to a Successful Submission (Do’s)

- Stay informed with new guidances
- Read the FDA Decision Summaries of predicates to help determine what may be requested
- Be organized and include page numbers, headings, and table of contents
- Proofread everything. Ensure consistency throughout submission. Tell the story of equivalence
- Read the labeling for claims not consistent with the proposed IFU
Tips to a Successful Submission (Don’ts)

• Avoid data dump
  – Follow the 510(k) Format Guidance
  – Provided info should have a purpose

• Expect a 510(k) review to be interactive. BE AVAILABLE to answer questions. A quick conversation between the reviewer and the sponsor can add clarity to a submission. This can speed up review.
510(k) Resources
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**

<table>
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<tr>
<th>Device Name</th>
<th>Applicant</th>
<th>510(k) Number</th>
<th>Decision Date</th>
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<tr>
<td>Locinox Total Vitamin D Test</td>
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<td>Architect 25-oh Vitamin D 5p02 Test</td>
<td>Abbott Laboratories</td>
<td>K153375</td>
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<td>K142351</td>
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The First LC-MS Device for Vitamin D Granted by FDA

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<tr>
<th>Device Classification Name</th>
<th>25-oh-vitamin D Mass Spectrometry Test System</th>
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<td>Clinical Chemistry</td>
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<td>Review Advisory Committee</td>
<td>Clinical Chemistry</td>
</tr>
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<td>Reclassification Order</td>
<td>Reclassification Order</td>
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<td>FDA Review Type</td>
<td>Post-NSE</td>
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[Decision Summary](#)
https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpmn/pmn.cfm
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
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.

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)

<table>
<thead>
<tr>
<th>Sample</th>
<th>Mean (ng/mL)</th>
<th>Repeatability</th>
<th>Within-Laboratory</th>
<th>Reproducibility</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>SD</td>
<td>%CV</td>
<td>SD</td>
</tr>
<tr>
<td>1</td>
<td>14.9</td>
<td>0.57</td>
<td>3.8%</td>
<td>1.05</td>
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<tr>
<td>2</td>
<td>13.7</td>
<td>0.65</td>
<td>4.7%</td>
<td>0.80</td>
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<tr>
<td>3</td>
<td>31.0</td>
<td>1.28</td>
<td>4.1%</td>
<td>2.03</td>
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<tr>
<td>4</td>
<td>67.5</td>
<td>3.58</td>
<td>5.3%</td>
<td>3.99</td>
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<td>5</td>
<td>100</td>
<td>6.37</td>
<td>6.3%</td>
<td>6.46</td>
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<tr>
<td>Native Patient Sample</td>
<td>28.4</td>
<td>1.44</td>
<td>5.1%</td>
<td>2.04</td>
</tr>
</tbody>
</table>

### K162298 (Immunoassay)

<table>
<thead>
<tr>
<th>Samples</th>
<th>N</th>
<th>Mean (ng/mL)</th>
<th>Repeatability</th>
<th>Within-Lab Precision</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>SD</td>
<td>%CV</td>
</tr>
<tr>
<td>QC (Low)</td>
<td>80</td>
<td>18.9</td>
<td>0.58</td>
<td>3.1</td>
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<tr>
<td>QC (Level 1)</td>
<td>80</td>
<td>38.7</td>
<td>1.02</td>
<td>2.6</td>
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<tr>
<td>QC (Level 2)</td>
<td>80</td>
<td>89.6</td>
<td>1.72</td>
<td>1.9</td>
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<tr>
<td>Serum 1</td>
<td>80</td>
<td>8.2</td>
<td>0.46</td>
<td>5.6</td>
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<tr>
<td>Serum 2</td>
<td>80</td>
<td>29.4</td>
<td>0.76</td>
<td>2.6</td>
</tr>
<tr>
<td>Serum 3</td>
<td>80</td>
<td>76.5</td>
<td>1.63</td>
<td>2.1</td>
</tr>
<tr>
<td>Plasma</td>
<td>80</td>
<td>25.2</td>
<td>0.44</td>
<td>1.8</td>
</tr>
</tbody>
</table>
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:

\[ y = 0.9974x + 1.1737 \quad R^2 = 0.998 \]

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:

\[ y = 1.0222x + 1.3862, \quad R^2 = 0.998 \]
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).
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).

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).

<table>
<thead>
<tr>
<th>n</th>
<th>Passing-Bablok regression results</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>Slope</td>
<td>1.008</td>
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<tr>
<td>Intercept</td>
<td>-0.3949</td>
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<td>Correlation Coefficient</td>
<td>0.991</td>
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<tr>
<td>Range (ng/mL)</td>
<td>5.6 – 133 ng/mL</td>
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</table>

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.

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.”
Summary and Conclusion

• A Class II device needs to demonstrate substantial equivalence to a legally marketed device in the US.
• You can do this through comparison with the predicate and through demonstrating equivalent analytical and clinical performance.
• Use the resources to see the performance of similar devices
• When in doubt, pre-submission