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

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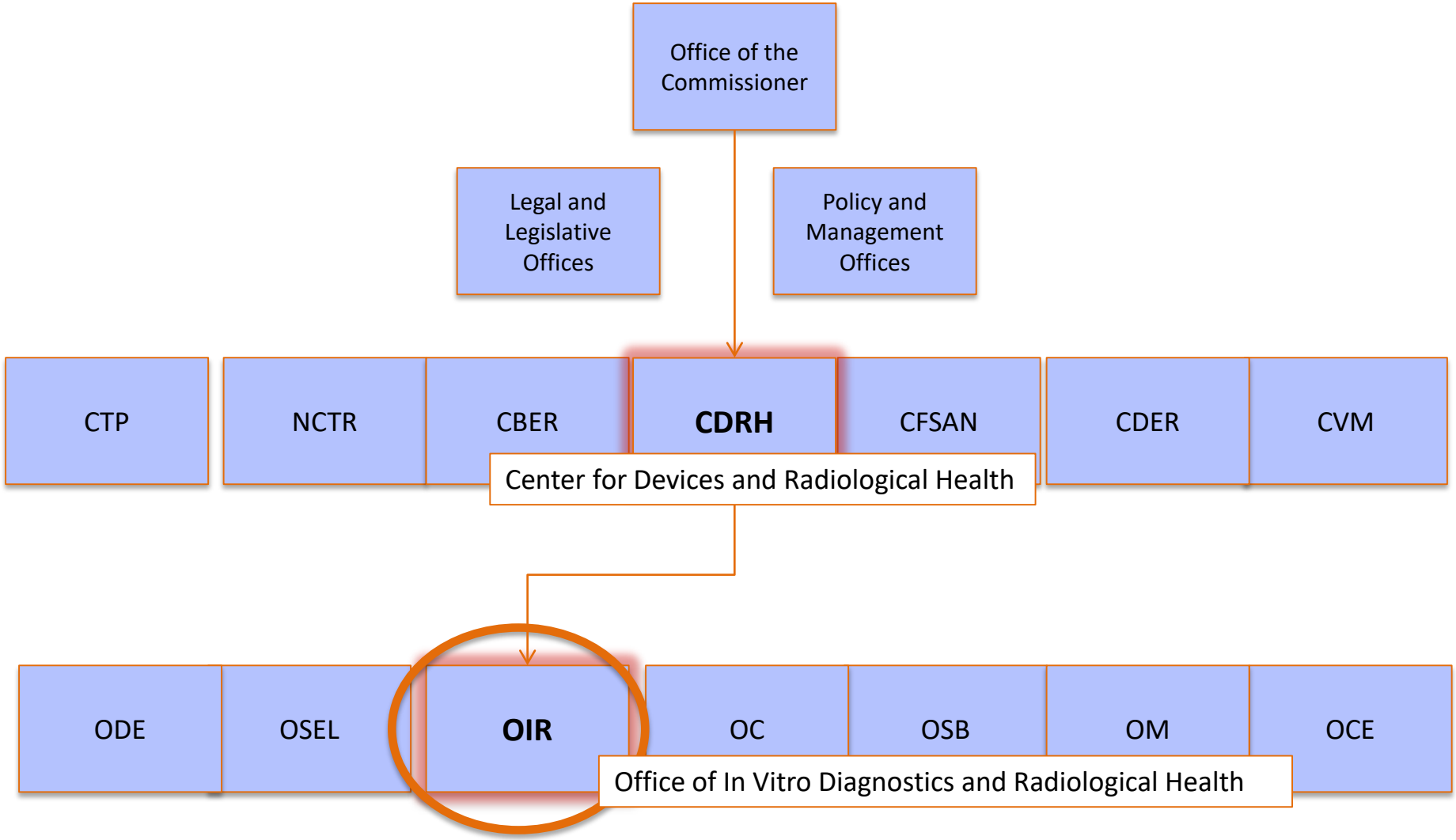
Disclaimer

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

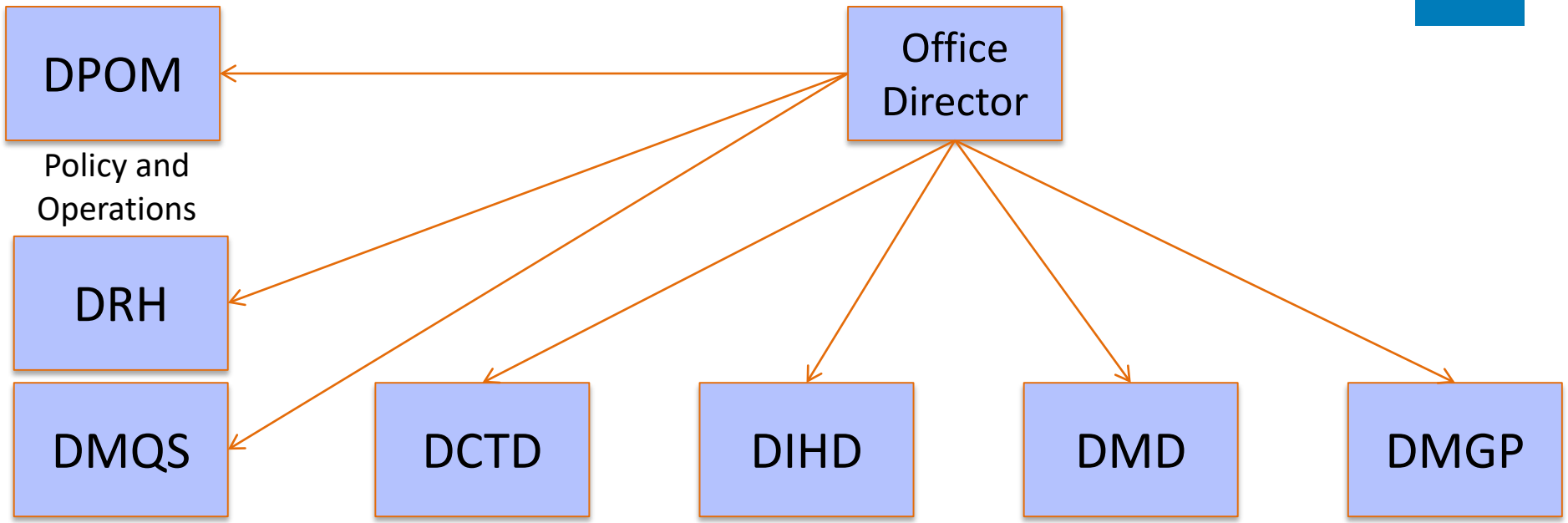
Disclosures

We have no financial conflicts to disclose

FDA Organizational Structure



OIR Organizational Structure



Radiological Health Review Divisions

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 microörganism Identification)
- Division of Molecular Genetics and Pathology (most cancers, companion diagnostics, NGS)

There are ~300 Employees in OIR Today

Medical Devices Are Evaluated According to Risk

- Class I: low risk (e.g., LIS, clinical concentrators)
- 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

	Class I	Class II		Class III
Risk	Low	Moderate		High
Clearance/ Approval	Not Required*	510(k)	De Novo	PMA
Pre-Submission	A free submission that allows Device Developers to get early feedback on their design and validation			
Investigational Device Exemption	A submission required for some devices that are being used in clinical trials			
Humanitarian Device Exemption	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.			

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

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 (sponsors may receive feedback on intended use during pre-submission process)
- Analytical and clinical validation studies should support the IU of the proposed device
- Clinical study should be conducted in the IU population

IU Example (cleared LC-MS assay)

Matrix

Analyte(s)

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.

Intended Population

Indication for Use

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
- Reference range (in normal population)

Clinical Performance

- Sensitivity/Specificity, Negative Predictive Value (NPV)/Positive Predictive Value (PPV) based on comparison to a gold standard (e.g., 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

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/

510(k)s (and De novos)

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

EXAMPLES OF CLASS I, II, III DEVICES HERE

Class I: Low Risk – tongue depressors, q-tips, LIS

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

Class III: High Risk Tests – PSA, 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
  - Submit a new 510(k)
  - PMA – approval of Class III devices
  - de novo

510(k) Remains the Principle Pathway to Obtain Market Authorization for Most Devices

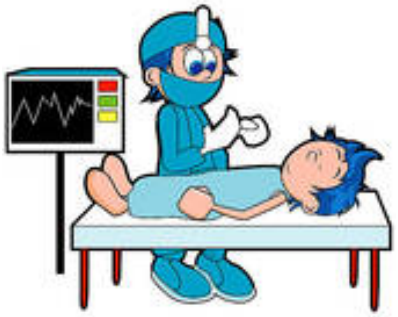
- The 510(k) program was established more than 40 years ago
  - CDRH receives ~3000 510(k)s per year
  - ~90% are found SE and go to market
- Premarket Notification (510(k)) procedures are found in 21 CFR Part 807, Subpart E
  - When a submission is required
  - Exemptions from notification
  - Format 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

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

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)

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 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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