U.S. FOOD & DRUG ADMINISTRATION

Welcome To Today's Webinar

Thanks for joining us!
We'll get started in a few minutes

Today's Topic:
FDA's Total Product Lifecyle Approach to IVDs

October 24, 2024

FDA's Total Product Lifecyle Approach to IVDs

Brittany Schuck, PhD
Deputy Office Director
Office of Health Technology 7: Office of In Vitro Diagnostic Devices
Office of Product Evaluation and Quality

Center for Devices and Radiological Health
U.S. Food and Drug Administration

Learning Objectives

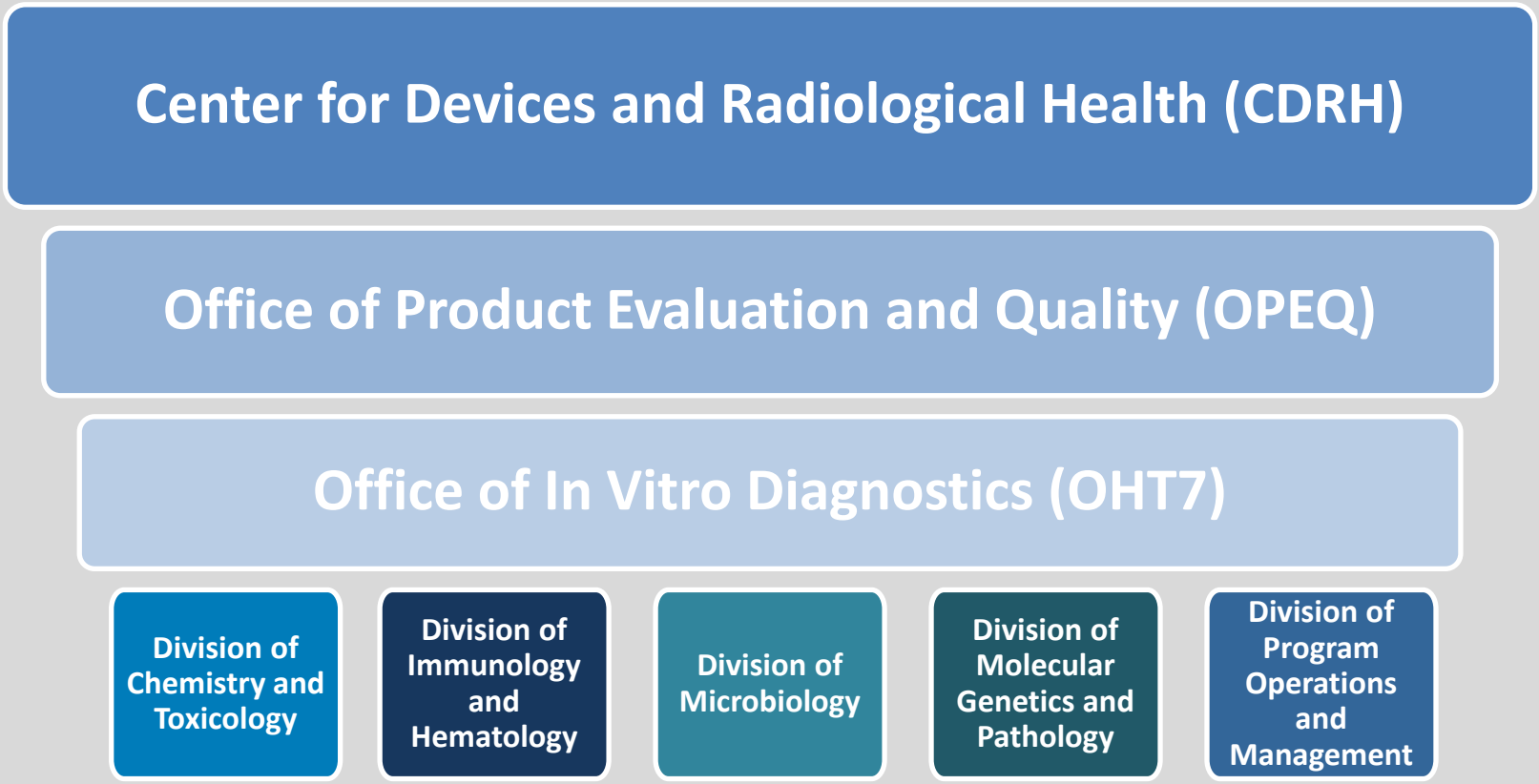
- Describe FDA's total product life cycle approach and FDA's roles and responsibilities in regulating in vitro diagnostic devices (IVDs) throughout the lifecycle of these products

- Describe the organizational units within FDA that are responsible for regulating IVDs

Center for Devices and Radiological Health

Our Mission: Protect and Promote Public Health

We assure that patients and providers have timely and continued access to **safe, effective, and high-quality** medical devices and safe radiation-emitting products.


Center for Devices and Radiological Health (CDRH)
Office of Product Evaluation and Quality (OPEQ)
Office of In Vitro Diagnostics (OHT7)
Division of Chemistry and Toxicology
Division of Immunology and Hematology
Division of Microbiology
Division of Molecular Genetics and Pathology
Division of Program Operations and Management

The Office of Health Technology 7: Office of In Vitro Diagnostics

Courtney H. Lias, PhD
Office Director

Brittany Schuck, PhD
Deputy Office Director

Ryan Lubert, J.D.
Acting Deputy Office Director

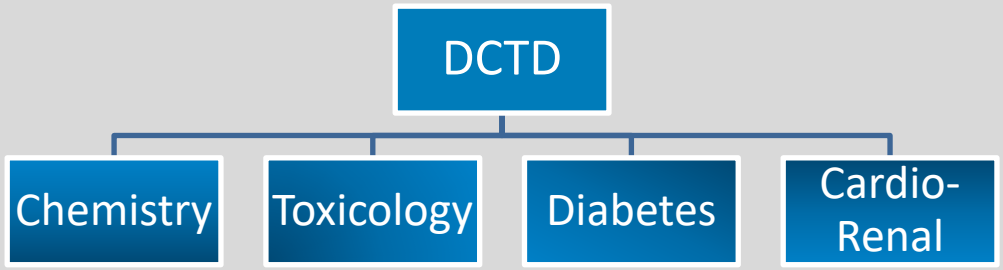
Toby Lowe
Acting Deputy Office Director

Sara Brenner, M.D.
Chief Medical Officer
Associate Director for Medical Affairs

Division of Chemistry and Toxicology Devices (DCTD)

Marianela Perez-Torres, PhD
Division Director

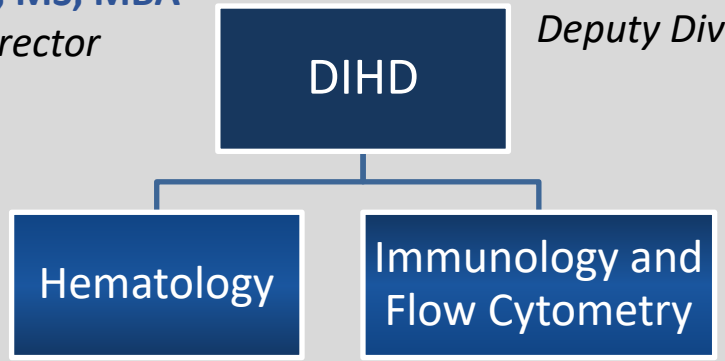
Paula Caposino, PhD
Deputy Division Director



Division of Immunology and Hematology (DIHD)

Lea Carrington, MS, MBA
Division Director

Takeesha Taylor-Bell
Deputy Division Director

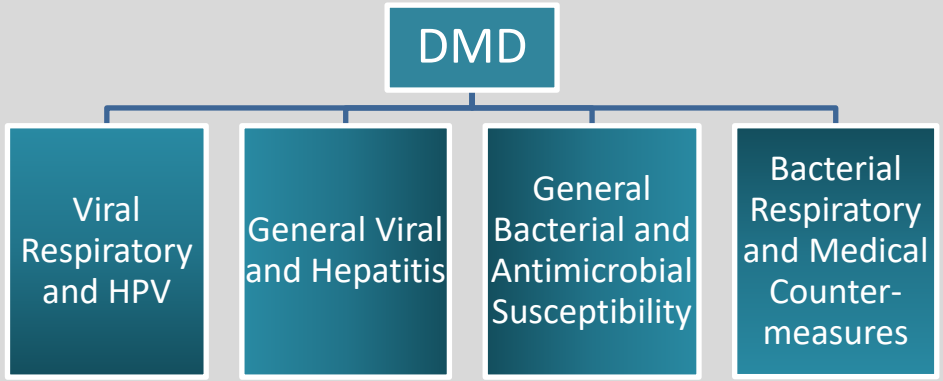


Division of Microbiology Devices (DMD)

Noel J. Gerald, PhD
Deputy Division Director

Uwe Scherf, PhD
Division Director

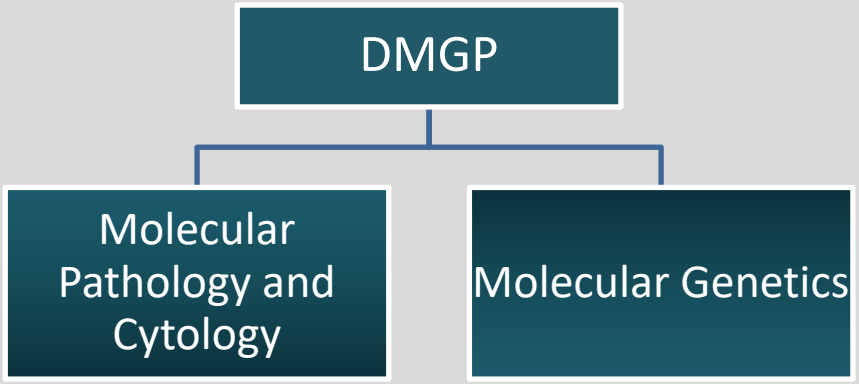
Joe Briggs, PhD
Deputy Division Director



Division of Molecular Genetics and Pathology (DMGP)

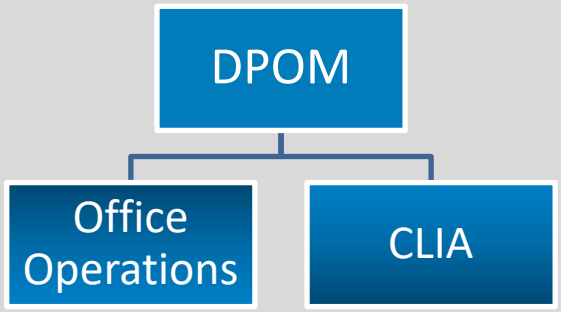
Soma Ghosh, PhD

Acting Division Director



Division of Program Operations and Management (DPOM)

Amy Zale
Division Director



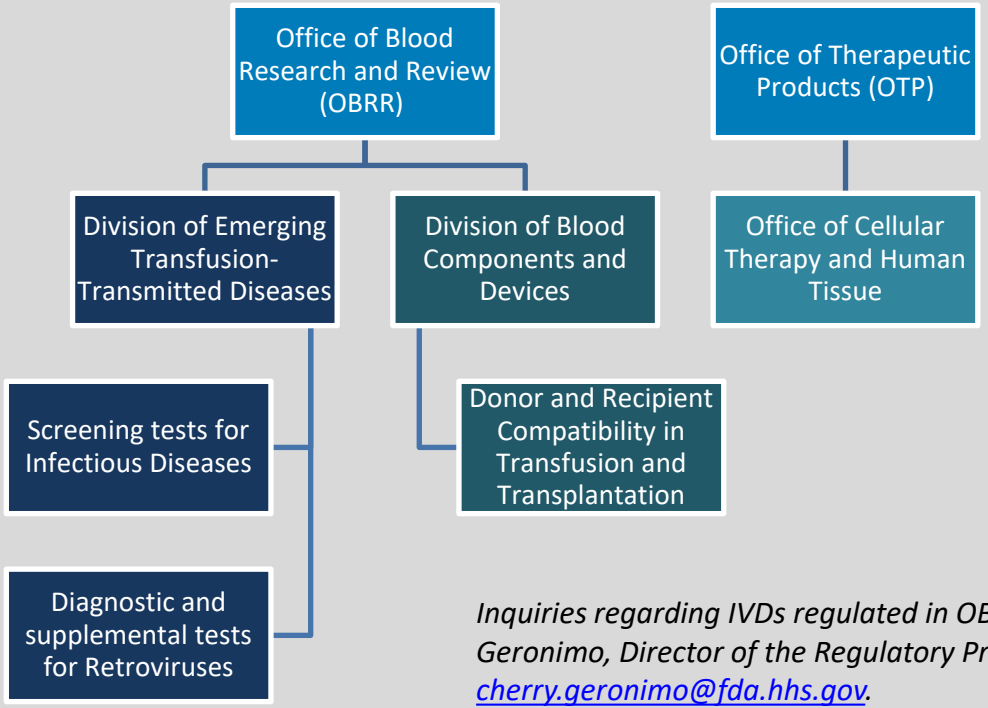
Benefits of the TPLC Approach

- Leverage knowledge of premarket data to inform our postmarket oversight and compliance decisions
- Leverage postmarket knowledge to make better informed premarket decisions
- Helps FDA respond to safety issues in a timely manner
- Helps FDA build strong and interactive relationships with test manufacturers so that challenges may be solved more efficiently, and FDA can support agile innovation of novel IVDs

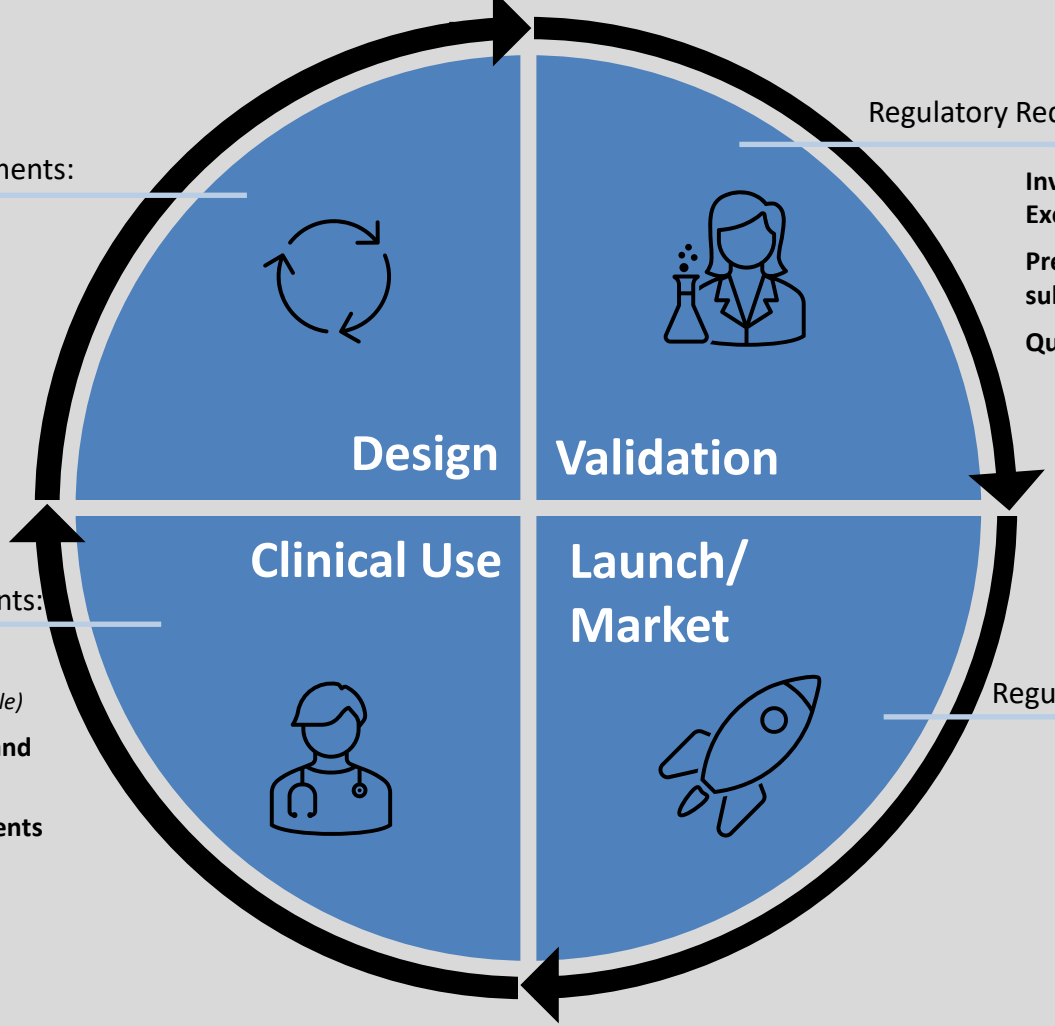
Center for Biologics Evaluation and Research (CBER)

CBER's mission is to ensure the safety, purity, potency, and effectiveness of biological products including **vaccines, allergenics, blood and blood products, and cells, tissues, and gene therapies** for the prevention, diagnosis, and treatment of human diseases, conditions, or injury.

Center for Biologics Evaluation and Research (CBER)



Inquiries regarding IVDs regulated in OBRR should be directed to Cherry Geronimo, Director of the Regulatory Project Manager Staff at cherry.geronimo@fda.hhs.gov.
Inquires regarding IVDs regulated in OTP should be directed to OTPRPMS@fda.hhs.gov.



Regulatory Requirements:

Quality System Requirements

Regulatory Requirements:

Investigational Device Exemption (IDE) *(as applicable)*

Premarket Review submission *(as applicable)*

Quality System Requirements

Regulatory Requirements:

Maintain Complaint Files

MDR Reporting *(as applicable)*

Reporting of Corrections and Removals *(as applicable)*

Quality System Requirements

Inspections

Registration & Listing

Labeling

Regulatory Requirements:

Registration & Listing

Labeling

Quality System Requirements

Pre-Submissions can be submitted at any time during the lifecycle of an IVD

Quality System

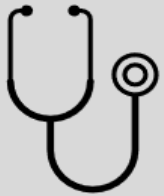
Manufacturers are required to establish and follow quality systems to help ensure the safety and effectiveness of their products on an ongoing basis.

Quality system requirements should be a consideration for manufacturers at every phase of the lifecycle of an IVD.

IVD Design

During the design of a device, manufacturers consider a number of factors when designing their device including:

Clinical Need Addressed by IVD



End User Preferences

IVD Validation

- Design and conduct studies to demonstrate the device meets user needs and its intended use such as:
  - Analytical validation
  - Clinical validation
- Engage with FDA during review(s), as applicable

Analytical Validation

What is analytical validation ?

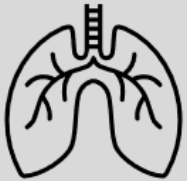
Analytical validation is the ability of the test to accurately and reliably measure or detect the analyte(s) it is intended to measure or detect

The specific information necessary to support the analytical validity of the test system will depend on:

- The intended use of the test system, including:
  - The purpose of the test
  - The disease or condition the test system is intended to diagnose, monitor, predict risk of, etc.
  - The analyte being detected or measured
  - The test method, including the technology, specimen type(s) and results reported
- The risks of wrong results to patients

Clinical Validation

What is clinical validation ?
Clinical validation is the accuracy and reliability with which the test identifies, measures, or predicts the presence or absence of a clinical condition or predisposition in a patient.



Similar to analytical validation, the specific information necessary to support the clinical validity of the test system will depend on a variety of factors including:

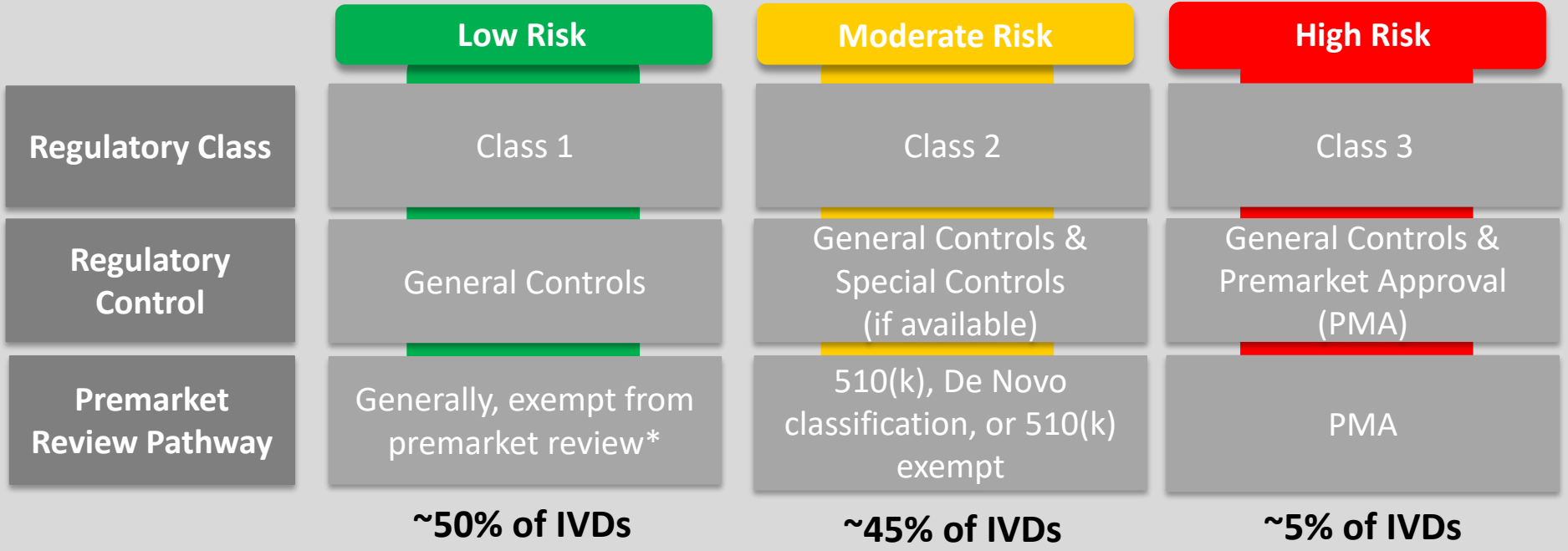
- The intended use of the IVD
- The risks of wrong results to patients

Clinical Investigations

- Validation studies for IVDs may include clinical investigations
- FDA will review the safety of clinical investigations of the subset of investigational use IVD studies that pose a significant risk to patients
- For those types of studies, an IDE application must be submitted to FDA and receive FDA approval before initiating that study.

Webinar discussing this topic coming 2025

Premarket Pathways & Submissions



*Class I reserved devices and devices that meet the limitations to exemption (for example, see 21 CFR 862.9) require premarket review through a 510(k)

Classify Your Medical Device | FDA

IVD Regulation

Webinar: In Vitro Diagnostic Product (IVD) Classification

FDA Review Times

Based on user fee agreements, FDA has agreed to generally perform their reviews in a specific period of time, though the length of time depends on the type of submission. The following are the review timeline goals based on the MDUFA V agreements:

Type of Submission	FDA's Review Goal
510(k)	90 FDA days
De Novo	150 FDA days
PMA	180 FDA days

Medical Device User Fee Amendments 2023 | FDA

CBER Specific Review Pathway

Certain CBER devices are regulated under Biologics License Application (BLAs) under Section 351 of the Public Health Service Act (PHS Act)

- Review goal within 10 calendar months for standard original BLAs
- Review goal within 6 calendar months for priority original BLAs

Enforcement Discretion and Exemption

Enforcement Discretion Policy: A policy in which FDA states its general intention to not enforce compliance with certain requirements such as (but not limited to) premarket notification.

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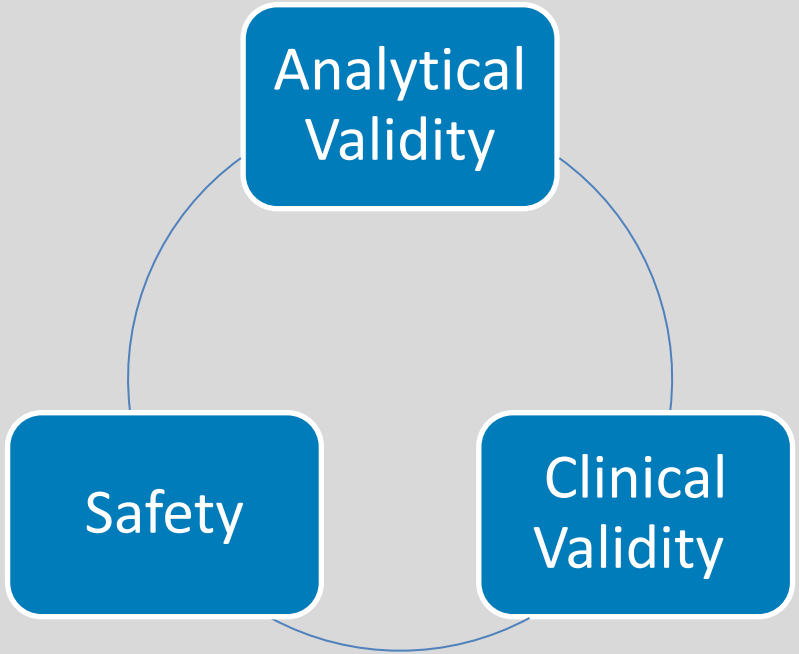
Exemption from premarket notification: All devices of a specific type are exempt from the requirements of premarket notification which is stated in the classification regulation for that device type.

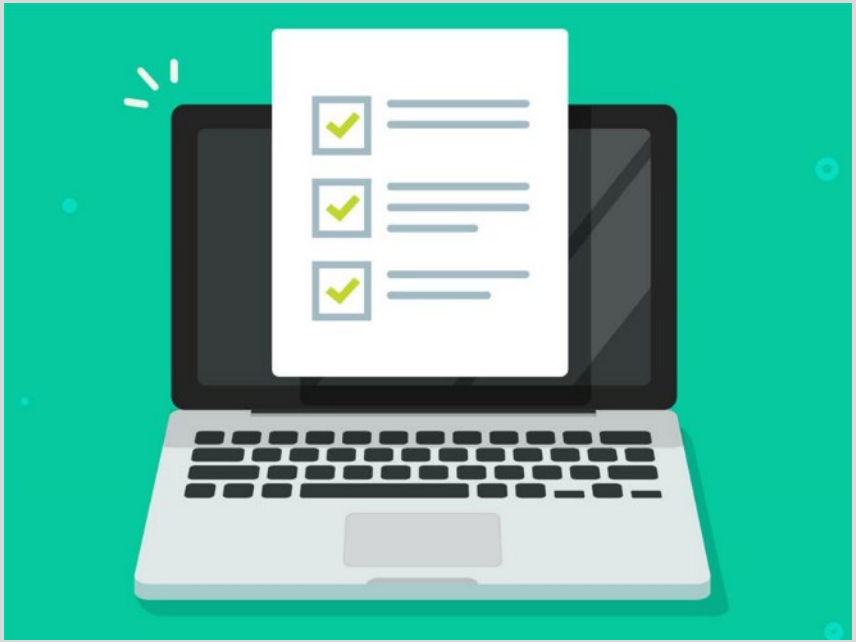
www.fda.gov/medical-devices/classify-your-medical-device/class-i-and-class-ii-device-exemptions

Premarket Review

In general, for IVDs, FDA reviews information supporting analytical validity, clinical validity, and safety prior to marketing.



Preparing for a Premarket Submission



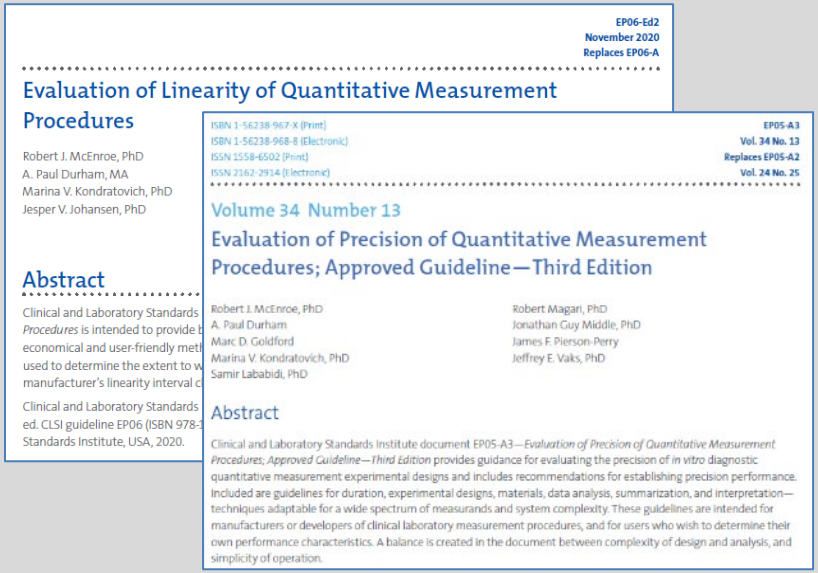
- FDA aims to be transparent about our expectations
- Resources are available as you design your validation studies and prepare your submission

FDA Guidance Documents

FDA Recognized Standards

FDA recognizes many useful standards, including CLSI guidelines.

[FDA-recognized standards database]



FDA Decision Summaries

For those devices which FDA has determined meet the statutory and regulatory requirements for marketing in the US, FDA has published summaries of the information used by FDA to make our decision

- CDRH 510(k) Database
- CBER 510(k) Database
- De Novo Database
- PMA Database

Type of information that is generally included in a decision summary:

- Type of test
- Intended use
- Predicate comparison
- Relevant Standards/Guidances
- Performance characteristics (analytical and clinical validation)
- Other information relevant to FDA's regulatory decision

Finding and Utilizing Decision summaries

510(k) Premarket Notification

FDA Home ▸ Medical Devices ▸ Databases

CDRH SuperSearch

510(k) | DeNovo | Registration & Listing | Adverse Events | Recalls | PMA | HDE | Classificati
CFR Title 21 | Radiation-Emitting Products | X-Ray Assembler | Medsun Reports | CLIA |

New Search

Device Classification Name	Acid, Folic, Radioimmunoassay
510(k) Number	K172201
Device Name	Atellica IM Folate Assay
Applicant	Siemens Healthcare Diagnostics Inc. 511 Benedict Avenue Tarrytown, NY 10591
Applicant Contact	Darius Daruwala
Correspondent	Siemens Healthcare Diagnostics Inc. 511 Benedict Avenue Tarrytown, NY 10591
Correspondent Contact	Darius Daruwala
Regulation Number	862.1295
Classification Product Code	CGN
Date Received	07/21/2017
Decision Date	04/12/2018
Decision	Substantially Equivalent (SE)
Regulation Medical Specialty	Clinical Chemistry
510k Review Panel	Clinical Chemistry
Summary	Summary
FDA Review	Decision Summary
Type	Traditional
Reviewed by Third Party	No
Combination Product	No
Recalls	CDRH Recalls

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

A. 510(k) Number:

k172201

B. Purpose for Submission:

New device

C. Measurand:

Folate

D. Type of Test:

Quantitative, competitive immunoassay

E. Applicant:

Siemens Healthcare Diagnostics Inc.

F. Proprietary and Established Names:

Atellica IM Folate Assay

G. Regulatory Information:

Product code	Classification	Regulation Section	Panel
CGN	II	21 CFR 862.1295 Folic acid test system	Clinical Chemistry 75

Utilizing Decision Summaries

M. Performance Characteristics (if/when applicable):

1. Analytical performance:

a. Precision/Reproducibility:

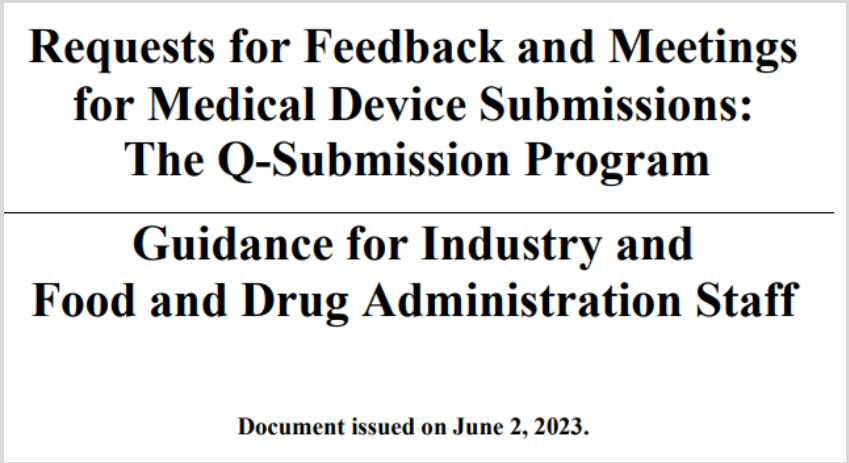
A 20-day precision study was performed according to CLSI EP5-A3. Four human serum and 5 whole blood samples and 2 levels of controls were tested using 3 lots of reagents. The samples were tested in duplicates per run, 2 runs per day for 20 working days. All 3 lots of reagents yielded similar results. The precision study summary is presented in the table below showing the results for one representative lot.

Sample Type	N	Mean (ng/mL)	Repeatability		Within-Lab Precision	
			SD	%CV	SD	%CV
Serum A	80	1.42	0.05	3.5	0.08	5.6
Serum B	80	4.13	0.10	2.4	0.24	5.9
Serum C	80	6.19	0.18	2.9	0.36	5.9
Serum D	80	9.23	0.24	2.6	0.6	6.5
Serum Control 1	80	2.82	0.09	3.3	0.17	6.1
Serum Control 2	80	5.43	0.14	2.5	0.35	6.4
Whole Blood Sample A	80	94.89	4.56	4.8	6.55	6.9
Whole Blood Sample B	80	153.11	4.40	2.9	11.21	7.3
Whole Blood Sample C	80	362.58	9.82	2.7	19.99	5.5
Whole Blood Sample D	80	563.94	19.34	3.4	35.18	6.2
Whole Blood Sample E	80	899.24	45.66	5.1	62.92	7.0
Whole Blood Control 1	80	77.24	2.68	3.5	5.48	7.1
Whole Blood Control 2	80	257.52	6.51	2.5	16.84	6.5

FDA Q-Submission Program

Various methods are available to submitters through which they can **request feedback in writing and/or a meeting** with the FDA regarding potential or planned medical device submissions

Q-Submission Guidance



Requests for Feedback and Meetings for Medical Device Submissions: The Q-Submission Program

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Guidance for Industry and Food and Drug Administration Staff

Document issued on June 2, 2023.

Premarket Review Process

For every review, the IVD manufacturer will know who their FDA reviewer is, and that person will serve as the main point of contact for questions during the review.

Interactive Review

During any part of the review process, reviewers may contact the manufacturer with questions about the information provided in the submission. This is called interactive review.

Requests for Additional Information

If there are questions that will take longer than a few days to answer, or would need a new study to be addressed, FDA may request additional information.

This formal Additional Information (AI) letter places the review on hold until the manufacturer responds.

A hold means that FDA's review clock is paused.

Manufacturer Response Times

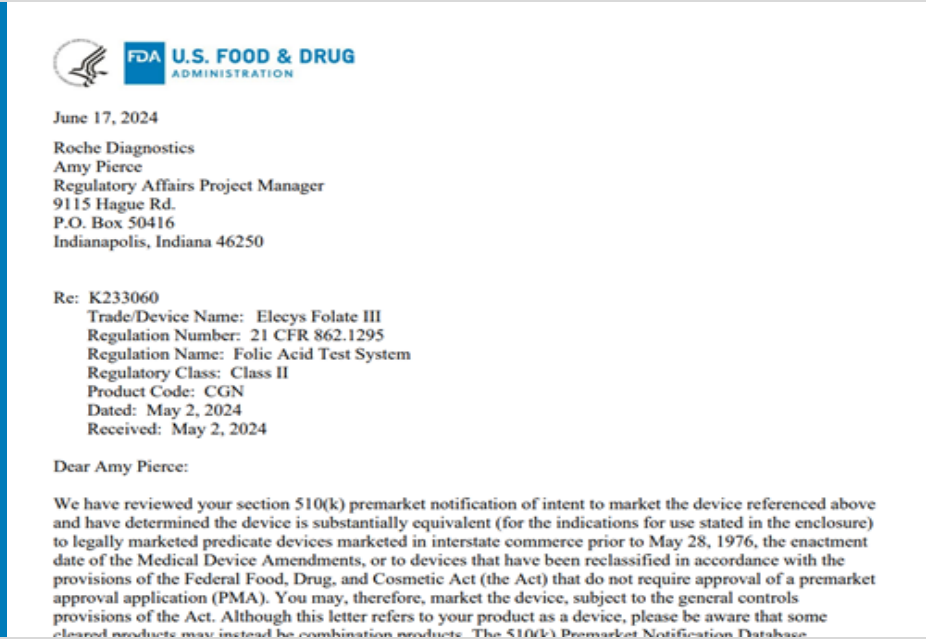
Additional Information requests indicate the amount of time manufacturers generally have to respond.

Type of Submission	Manufacturer Response Time
510(k)	180 days
De Novo	180 days
PMA	360 days

FDA and applicants share the responsibility for achieving the objective of reducing the average Total Time to Decision, while maintaining standards for safety and effectiveness.

Review Conclusion

At the end of the review, a decision letter will be sent by the lead reviewer via email stating FDA's decision on the submission.



FDA U.S. FOOD & DRUG ADMINISTRATION

June 17, 2024

Roche Diagnostics
Amy Pierce
Regulatory Affairs Project Manager
9115 Hague Rd.
P.O. Box 50416
Indianapolis, Indiana 46250

Re: K233060
Trade/Device Name: Elecys Folate III
Regulation Number: 21 CFR 862.1295
Regulation Name: Folic Acid Test System
Regulatory Class: Class II
Product Code: CGN
Dated: May 2, 2024
Received: May 2, 2024

Dear Amy Pierce:

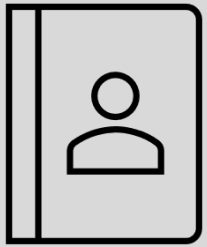
We have reviewed your section 510(k) premarket notification of intent to market the device referenced above and have determined the device is substantially equivalent (for the indications for use stated in the enclosure) to legally marketed predicate devices marketed in interstate commerce prior to May 28, 1976, the enactment date of the Medical Device Amendments, or to devices that have been reclassified in accordance with the provisions of the Federal Food, Drug, and Cosmetic Act (the Act) that do not require approval of a premarket approval application (PMA). You may, therefore, market the device, subject to the general controls provisions of the Act. Although this letter refers to your product as a device, please be aware that some cleared products may instead be combination products. The 510(k) Premarket Notification Database

Launch/Market

- After a successful decision on the premarket submission, the manufacturer can begin to market the device, provided all other applicable requirements are met.

Registration and Listing

A device manufacturer **registers** their establishment and **lists** their device



Establishment Registration & Device Listing - FDA

Clinical Use and Surveillance

- Annual registration and listing
- Labeling requirements
- Adverse event reporting (MDRs)
- Continued compliance with QS requirements
- Reporting of corrections and removals

Webinar - In Vitro Diagnostic Products (IVDs) - MDR Requirements, Correction and Removal Reporting Requirements, and Quality System Complaint Requirements

Clinical Use and Surveillance

Inspections

Device manufacturers may be inspected by FDA.

These inspections are performed by FDA investigators.

Shortages

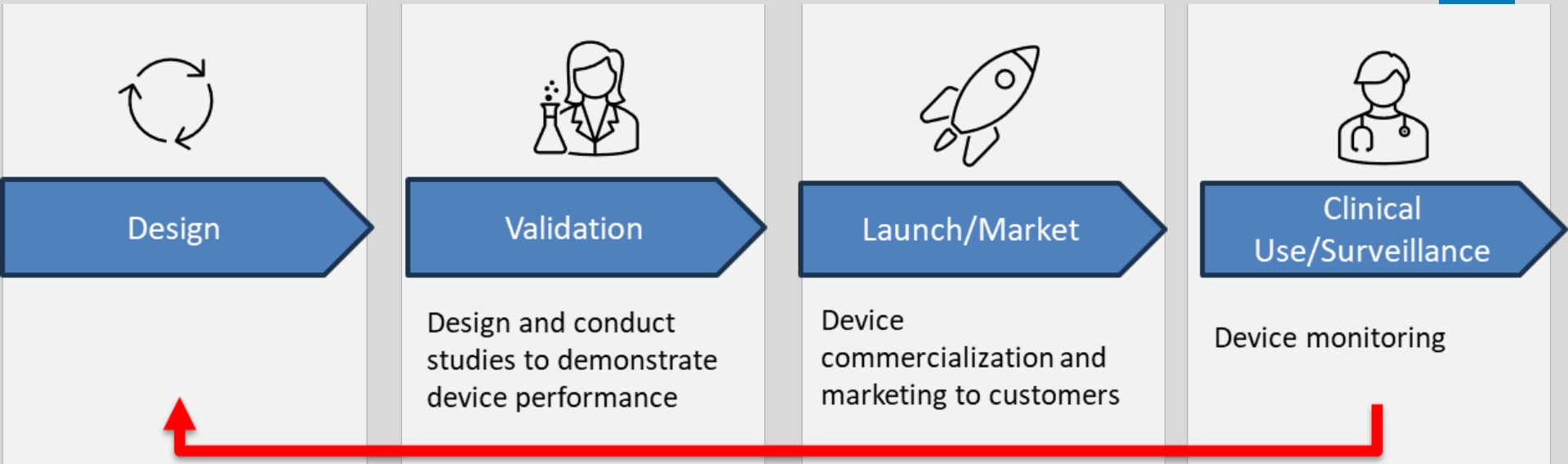
FDA works with device manufacturers to identify shortages and to minimize the impact of shortages on the public health system.

CDRH: Medical Device Shortages List | FDA

CBER: CBER-Regulated Products: Current Shortages | FDA

Safety Communications

FDA may also issue safety communications or letters to healthcare providers to publicly share information about specific risks related to specific devices or types of devices or other issues identified through this TPLC framework that may affect public health.



Information obtained during the clinical use and surveillance phase of a product life cycle can inform future device design and premarket reviews

Device Modifications

Manufacturers may make changes to their device after marketing for various reasons such as:

- To improve performance, speed, etc.
- To update to new technology
- To fix a problem

[Deciding When to Submit a 510(k) for a Change to an Existing Device]
[Modifications to Devices Subject to Premarket Approval (PMA)]

Surveillance data informs FDA Review

Surveillance information is used to identify issues with marketed products. Can lead to potential actions including:

- Public communications
- Premarket review considerations
- Design changes

Biotin Interference (% Bias for Samples Containing Various Concentration of Biotin)								
Sample and Folate (ng/mL)	Biotin Concentration (ng/mL)							
	1	5	19	38	75	150	300	600
Serum 9.23	1.4%	-1.1%	6.9%	4.7%	20.2%	>AMR*	>AMR*	>AMR*
Serum 17.37	1.3%	1.3%	3.6%	8.3%	35.3%	>AMR*	>AMR*	>AMR*
Whole Blood 12.76	-7.0%	-8.4%	-8.8%	-5.7%	-3.5%	-1.1%	49.6%	68.0%
Whole Blood 18.47	0.1%	4.5%	-0.2%	4.4%	7.8%	12.7%	>AMR*	>AMR*

*Interference could not be calculated because the results of the biotin spiked samples were above the claimed analytical measuring range.

FDA began requesting biotin interference testing and working with manufacturers to provide labeling on biotin interference when applicable

- Do not test samples from patients who take high doses of biotin. If biotin interference is suspected, follow your established internal procedures to investigate the interference or test with an alternate assay that is not affected by biotin interference.

Summary

- FDA maintains oversight over the entire TPLC of an IVD and may interact with the manufacturer at various points
- CDRH and CBER staff have significant expertise across the TPLC of IVDs and there are many opportunities for feedback from FDA as manufacturers work to comply with applicable regulatory requirements

Resources

Slide Number	Cited Resource	URL
22	How to Classify Your Medical Device	www.fda.gov/medical-devices/overview-device-regulation/classify-your-medical-device
22	Class I (reserved) devices	www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpcd/3151.cfm
22	Webinar: In Vitro Diagnostic Product (IVD) classification	www.fda.gov/medical-devices/medical-devices-news-and-events/webinar-in-vitro-diagnostic-product-ivd-classification-07162024
22	IVD Regulation	www.fda.gov/medical-devices/ivd-regulatory-assistance/overview-ivd-regulation
23	Medical Device User Fee Amendments 2023	www.fda.gov/industry/medical-device-user-fee-amendments-mdufa/medical-device-user-fee-amendments-2023
25	Class I/II Exemptions	www.fda.gov/medical-devices/classify-your-medical-device/class-i-ii-exemptions
27	FDA Guidance Documents Database	www.fda.gov/medical-devices/device-advice-comprehensive-regulatory-assistance/guidance-documents-medical-devices-and-radiation-emitting-products
28	FDA Recognized Consensus Standards	www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfStandards/search.cfm

Resources

Slide Number	Cited Resource	URL
29	Premarket Notification 510(k)	www.fda.gov/medical-devices/premarket-submissions/premarket-notification-510k
29	De Novo Database	www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMN/denovo.cfm
29	Premarket Approval	www.fda.gov/medical-devices/premarket-submissions/premarket-approval-pma
29	CBER 510(k) Database	www.fda.gov/vaccines-blood-biologics/substantially-equivalent-510k-device-information/cleared-510k-submissions-supporting-documents
32	Q-Submission Guidance	www.fda.gov/regulatory-information/search-fda-guidance-documents/requests-feedback-and-meetings-medical-device-submissions-q-submission-program
39	Establishment Registration & Device Listing	www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfRL/rl.cfm
40	Webinar - In Vitro Diagnostic Products (IVDs) - MDR Requirements, Correction and Removal Reporting Requirements, and Quality System Complaint Requirements	www.fda.gov/medical-devices/medical-devices-news-and-events/webinar-in-vitro-diagnostic-products-ivds-mdr-requirements-correction-and-removal-reporting
41	CDRH Medical Device Shortages List	www.fda.gov/medical-devices/medical-device-supply-chain-and-shortages/medical-device-shortages-list

Resources

Slide Number	Cited Resource	URL
41	CBER Shortages List	www.fda.gov/vaccines-blood-biologics/safety-availability-biologics/cber-regulated-products-current-shortages
43	Deciding when to submit a 510(k) for a Change to an Existing Device	www.fda.gov/regulatory-information/search-fda-guidance-documents/deciding-when-submit-510k-change-existing-device
43	Modification to Devices Subject to PreMarket Approval (PMA)	www.fda.gov/regulatory-information/search-fda-guidance-documents/modifications-devices-subject-premarket-approval-pma-pma-supplement-decision-making-process
Q&A	Breakthrough Devices Program | FDA	www.fda.gov/medical-devices/how-study-and-market-your-device/breakthrough-devices-program
Q&A	In Vitro Diagnostic (IVD) Device Studies - Frequently Asked Questions | FDA	www.fda.gov/regulatory-information/search-fda-guidance-documents/in-vitro-diagnostic-ivd-device-studies-frequently-asked-questions
Q&A	Investigational Device Exemption (IDE) | FDA	www.fda.gov/medical-devices/premarket-submissions-selecting-and-preparing-correct-submission/investigational-device-exemption-ide

Upcoming Webinar

Date
December 3, 2024

Time
1:00 - 2:00 pm ET

Topic
Registration & Listing Requirements for IVDs, Including LDTs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Thanks for Joining Today!

- **Presentation and Transcript will be available at CDRH Learn**
  - www.fda.gov/Training/CDRHLearn
- **Additional questions about today's webinar**
  - Email: DICE@fda.hhs.gov
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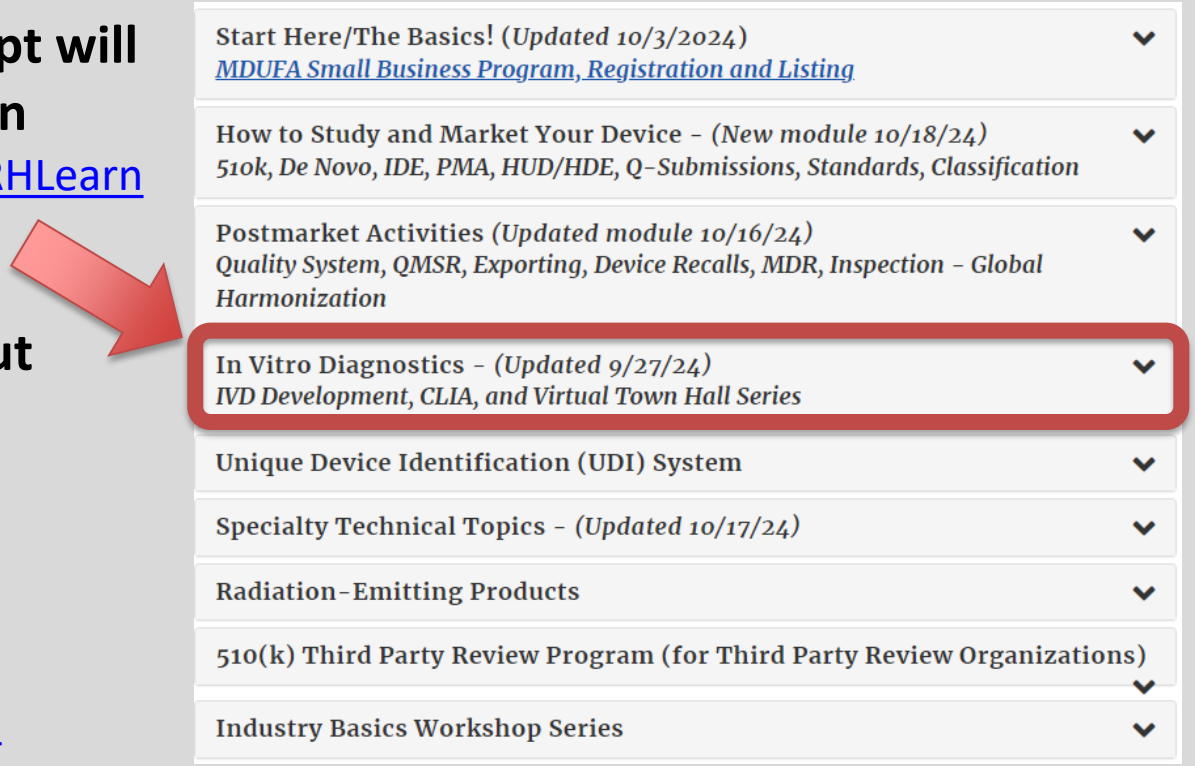


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