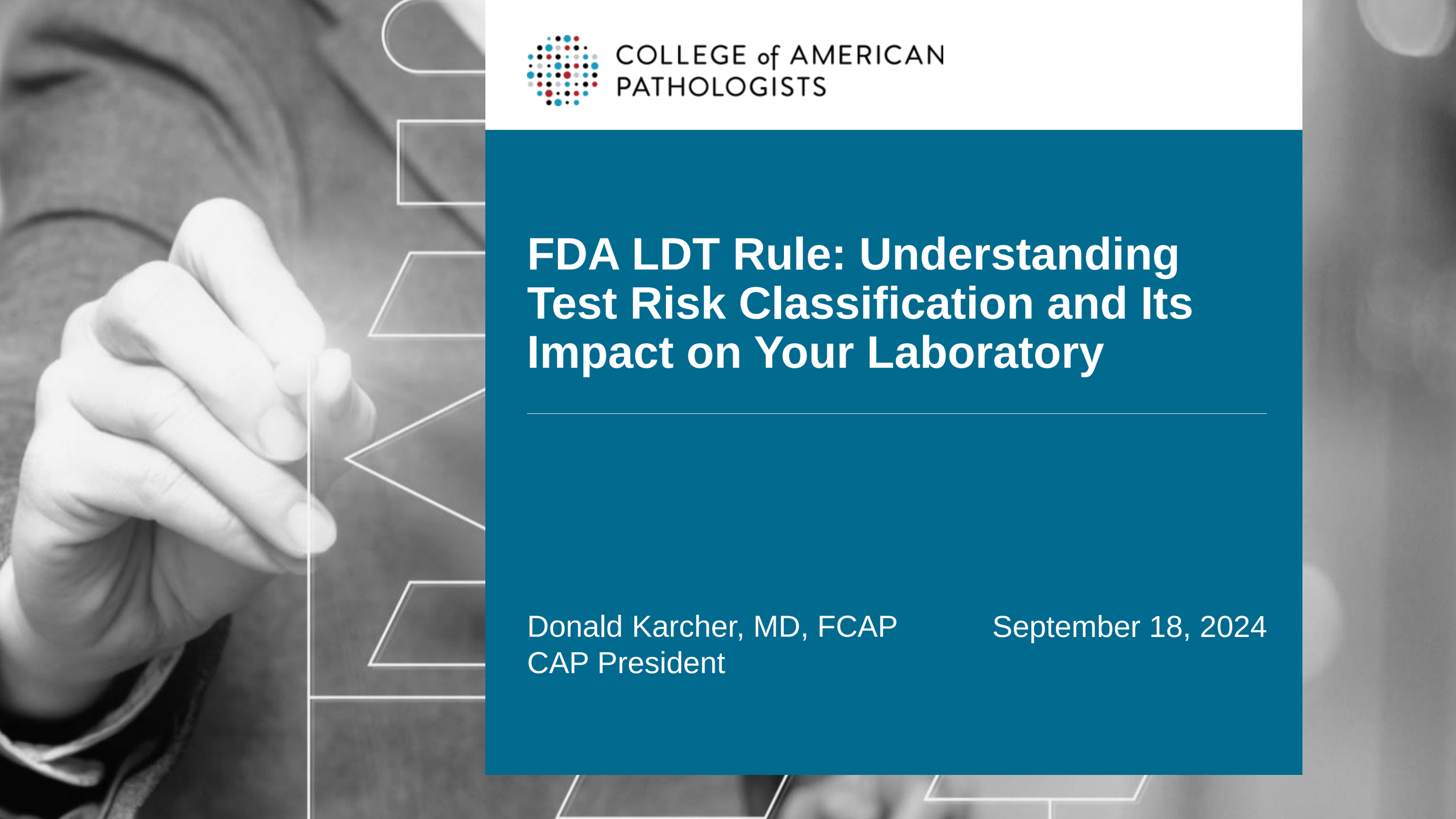


COLLEGE of AMERICAN PATHOLOGISTS

FDA LDT Rule: Understanding Test Risk Classification and Its Impact on Your Laboratory

Donald Karcher, MD, FCAP
CAP President

September 18, 2024

Today’s Presenters

Donald S. Karcher, MD, FCAP

- President, College of American Pathologists
- Board-certified in anatomic, clinical, and hematopathology
- Professor and Immediate Past Chair of Pathology, George Washington University Medical Center, where he’s been a faculty member since 1984
- An academic pathologist who has been active in many national and international medical and pathology organizations
- 30+ years as a CAP leader
- Served as Association of Pathology Chairs (APC) President from 2014 to 2016
- Published over 100 peer-reviewed articles and abstracts, co-authored several book chapters, and co-edited six books spanning his subspecialties

Today’s Presenters

Timothy Stenzel, MD, PhD

- CEO Grey Haven LLC
- Board certified in pathology and genetics
- Former Director of the FDA’s Office of In Vitro Diagnostics
- Over 25 years in executive leadership, innovation, companion diagnostics, molecular diagnostics, molecular genetics, immunology, infectious diseases, surgical pathology, and laboratory medicine
- Received his MD and PhD in microbiology and immunology from Duke University
- Founded the Duke Clinical Molecular Diagnostics laboratory; clinical and research laboratories in Japan and China respectively, and molecular diagnostics at QuidelOrtho

Background: FDA Oversight of LDTs

- Oversight of LDTs by FDA has been an issue for more than 10 years.
- When a legislative solution (VALID Act) didn’t pass in 2022, FDA said they would regulate LDTs under their existing statutory authority.
- FDA released proposed oversight rule on Sept. 29, 2023, and final rule on April 29, 2024.

Background: FDA Oversight of LDTs

- **Basic provisions:**
  - **Employs a three-tiered, risk-based structure.**
  - **Phases out general enforcement discretion in five stages by May 2028.**
- **While the FDA regulation includes exemptions, most LDTs must meet requirements for at least Stages 1, 2 , and parts of 3.**

Stage 1

- **May 6, 2025**
- Compliance with medical device reporting, correction and removal reporting, and quality system requirements for complaints.

Stage 2

- **May 6, 2026**
- Compliance with registration and listing, labeling, and investigational use requirements.

Stage 3

- **May 6, 2027**
- Compliance with all quality system requirements.

Stage 4

- **November 6, 2027**
- Pre-market review for high-risk LDTs.

Stage 5

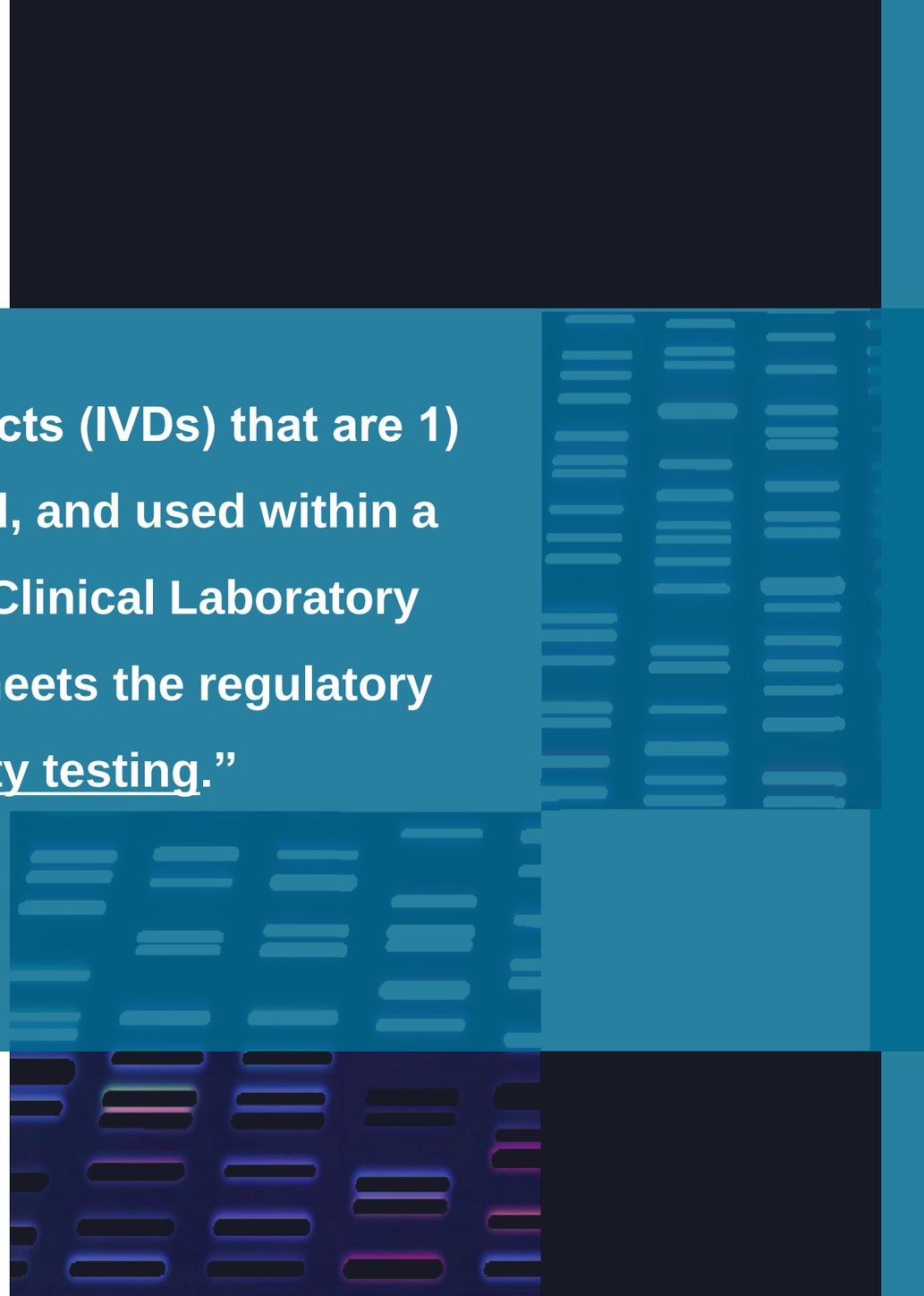
- **May 6, 2028**
- Pre-market review for moderate- and low-risk LDTs.

Background: CAP Advocacy on LDT Oversight

- CAP advocacy principles on LDT oversight:
  - Protect patients.
  - Allow for continued innovation of new tests.
  - Develop a framework that is the least burdensome and costly for pathologists and their laboratories.
- We oppose the final FDA rule.
  - CAP supports legislation to reduce regulatory burdens on laboratories.
  - CAP supports legal efforts to stop the regulation's implementation.
- At the same time, the CAP will continue to prepare members and laboratories to comply with FDA regulations.

Background: What is an LDT?

- The FDA defines LDTs as “in vitro diagnostic products (IVDs) that are 1) intended for clinical use; 2) designed, manufactured, and used within a single clinical laboratory that is certified under the Clinical Laboratory Improvement Amendments of 1988 (CLIA); and 3) meets the regulatory requirements under CLIA to perform high complexity testing.”
- By definition, all LDTs are high complexity.



Background: FDA Test Risk vs. CLIA Test Complexity

- FDA test risk classification is different from CLIA test complexity.
- CLIA regulations categorize tests as moderate or high complexity.
- CLIA categorization criteria (determined during FDA test authorization):
  - Knowledge needed to perform
  - Training and experience needed to perform
  - Reagents and materials preparation
  - Characteristics of operational steps
  - Calibration, quality control, and proficiency testing materials
  - Test system troubleshooting and equipment maintenance required
  - Interpretation and judgement required

Background: FDA Risk Classification

- FDA uses a system based on patient risk to classify medical devices/tests:
  - Low Risk (Class I)
  - Moderate Risk (Class II)
  - High Risk (Class III)
- The FDA's classification is based on the "intended use" and risk posed by the device/test to patients.

Understanding the Impact of the FDA's LDT Risk Classification on Your Laboratory

Tim Stenzel, MD, PhD, Former Director, FDA Office of In Vitro Diagnostics
Grey Haven LLC

Disclaimers & Notes

Notes:

1) I will generally use lay/non-FDA language in this presentation to facilitate understanding of the concepts. However, FDA will typically use legal terms for most items. This is a new language to many and sometimes difficult to decipher. Most of the language is defined by law and regulations and is not intentionally meant to complicate understanding.
2) Much of the content in this presentation mirrors an FDA Webinar on this topic held on July 16, 2024. The first link at the end of this presentation is to that FDA Webpage.
3) I will focus my presentation on clinical laboratory tests.

Agenda

- Reclassification (Down) of Some CDx tests and Other IVDs
- Final LDT Rule and Potential Legislation
- FDA Classification Process/System
- Determining Classifications with Examples
- Communications with FDA
- Helpful Links
- Q&A

Down Classification of Some CDx Tests and Other IVDs

- On January 31, 2024 the FDA made known its decision to initiate a reclassification process for most IVDs that are currently Class III to Class II
- The FDA has prior exempted more than 1,000 IVDs from FDA review
- FDA reclassified HCV on November 19, 2021. Per Timothy Stenzel….'Today's action allows manufacturers of….HCV tests….to seek marketing clearance…rather than…a PMA"…
- In 2023, FDA began the process of reclassifying HBV and certain other IVDs to class II

FDA reclassification process (usually down but can be up)

The original classification of a device can be changed through reclassification.

The FDA follows a process that includes issuing a proposed order, convening an expert panel, receiving and considering public comment, and issuing a final order.

The process usually takes ~2 years.

Final LDT Rule and Potential Legislation

- The Final rule was announced on 29APR2024, “grandfather” ended 06MAY2024, in force 60 days after publishes ~06JUL2024. Makes one change to the definition of an IVD product “including when the manufacturer of these products is a laboratory.”
- Phaseout Period (by end of each period)

  1 Year – comply with MD(AE) reporting and reporting of corrections and removals

  2 Years – comply with labeling, registration and listing, and investigational use requirements

  3 Years – QS [v light, light and full] – records and sometimes design controls and purchasing controls

  3.5 Years – comply with **high risk (class III)** premarket review requirements (PMA)

  4 Years – comply with **moderate and low risk** premarket review requirements moderate and low
- Enforcement Discretion (ED) continues for Forensic, HLA, PH Surveillance and pre-1976 type LDTs (manual)
- Excluded from ED – EUAs, DTC (stay tuned for more details) and donor screening

FDA Classification System

The FDA uses a risk-based classification system for all medical devices, including Laboratory Developed Tests/IVDs, into Classes I, II, or III according to the level of regulatory control (mitigations) that are deemed necessary by the FDA to ensure accurate results.

The classification of a clinical laboratory test determines the appropriate premarket regulatory process.

The FDA also examines the intended use of the test when making a classification decision.

Indications for/Intended use

Purpose of the test – aid in diagnosis, CDx, MRD, etc

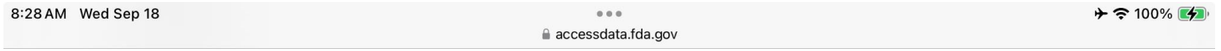
Disease or condition the test is designed for – Leukemia, diabetes, etc

Test methodology used – PCR, NGS, novel, etc

Intended patient population for the test – Ages, high risk, low risk, cancer, etc

Where testing the test is performed – LDTs will be performed in high complexity laboratories

Indications for/Intended use example



H. Indications for Use:

1. **Indications for Use:**
   The MSK-IMPACT assay is a qualitative in vitro diagnostic test that uses targeted next generation sequencing of formalin-fixed paraffin-embedded tumor tissue matched with normal specimens from patients with solid malignant neoplasms to detect tumor gene alterations in a broad multi gene panel. The test is intended to provide information on somatic mutations (point mutations and small insertions and deletions) and microsatellite instability for use by qualified health care professionals in accordance with professional guidelines, and is not conclusive or prescriptive for labeled use of any specific therapeutic product. MSK-IMPACT is a single-site assay performed at Memorial Sloan Kettering Cancer Center.

2. **Special conditions for use statement(s):**

   For prescription use.

   For in vitro diagnostic use.

3. **Special instrument requirements:**

   Illumina HiSeq™ 2500 Sequencer (qualified by MSK)

I. Device Description:
A description of required equipment, software, reagents, vendors, and storage conditions

Risk levels

Low Risk – Class I	Moderate Risk – Class II	High Risk – Class III
Tests with minimal risk for harm	Mid range risk for harm	Tests to support or sustain human life which present a potential for unreasonable risk of harm

For tests already classified look to the FDA databases for their classifications

A straightforward way for a test developer to determine the classification of a test that has already been classified by FDA is to search the FDA product classification database. There are separate databases for 510(k), PMA, and De Novo submissions.

May also be helpful in understanding what specific IVDs fall within a given device type and how such IVDs are regulated.

What if your specific sample/specimen type or technology is not in the data

Usually, it does not alter the classification except for when the sample/specimen type or technology is novel. However, where differences in specimen type or technology between a subject IVD test system and those specified in a classification regulation raise different questions of safety and effectiveness, the classification regulation describing use for a specific specimen type or technology would not be appropriate for a different specimen type or technology. If manufacturers have questions regarding the classification of a specific test, they can submit a Pre-Submission or 513(g) request to obtain specific feedback.

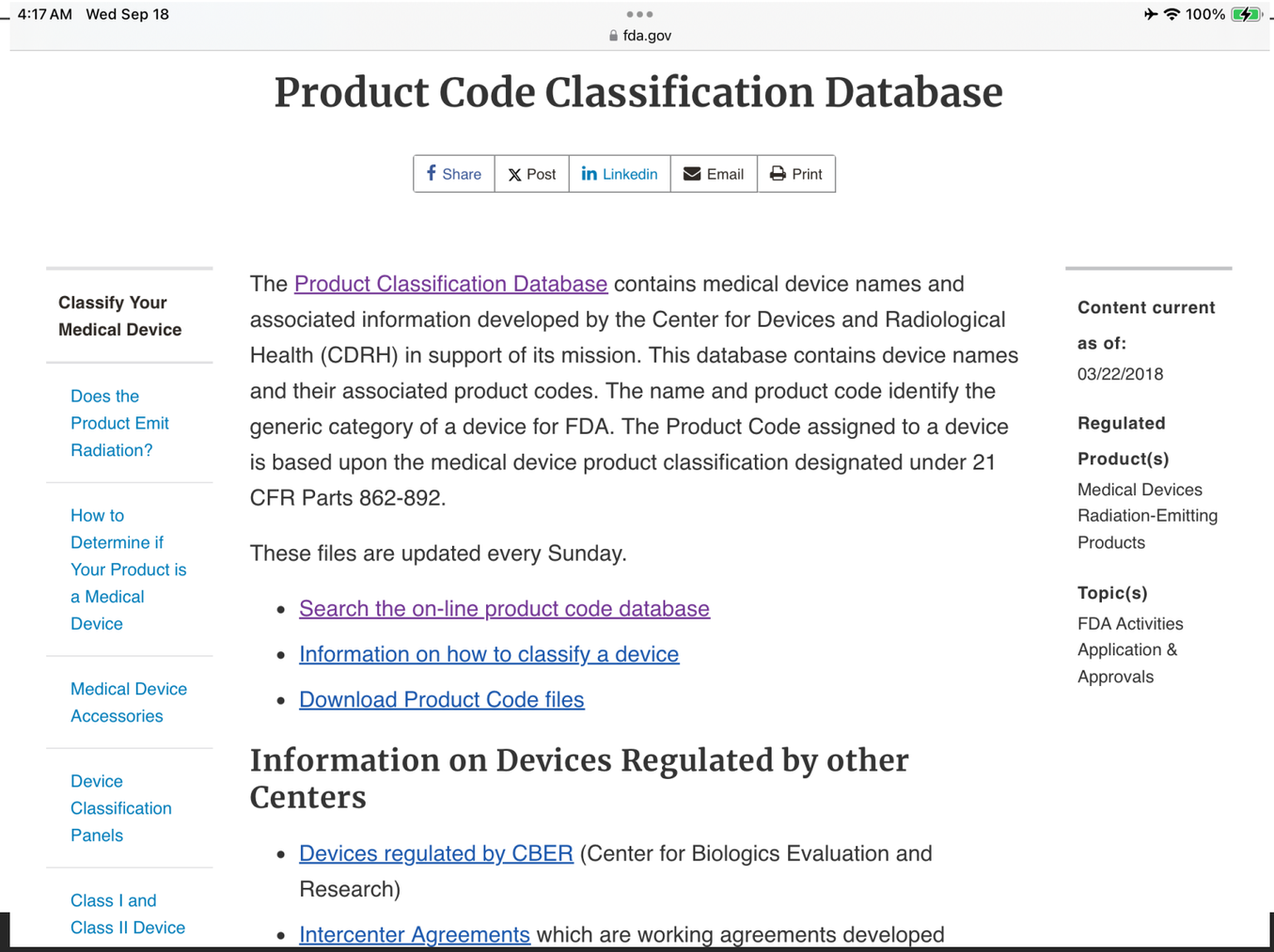
For tests not already classified (typically novel tests)

An IVD may be of a type that has not already been classified by FDA and, therefore, would not be in the product classification database. As a reminder, device types that have not been classified by FDA previously, and that were not on the market prior to the enactment of the Medical Device Amendments on May 28, 1976, are automatically Class III unless they are reclassified by the FDA. If an IVD has not been classified, manufacturers should assess the risk of their IVD and submit the appropriate premarket submission based on the assessed risk. If the manufacturer believes their IVD is high risk, a PMA is likely required. If the manufacturer believes their IVD is low or moderate risk, the IVD may be eligible for De Novo classification. The De Novo process provides a pathway to Class I or Class II classification for medical devices for which general controls or general and special controls provide a reasonable assurance of safety and effectiveness but for which there is no legally marketed device.

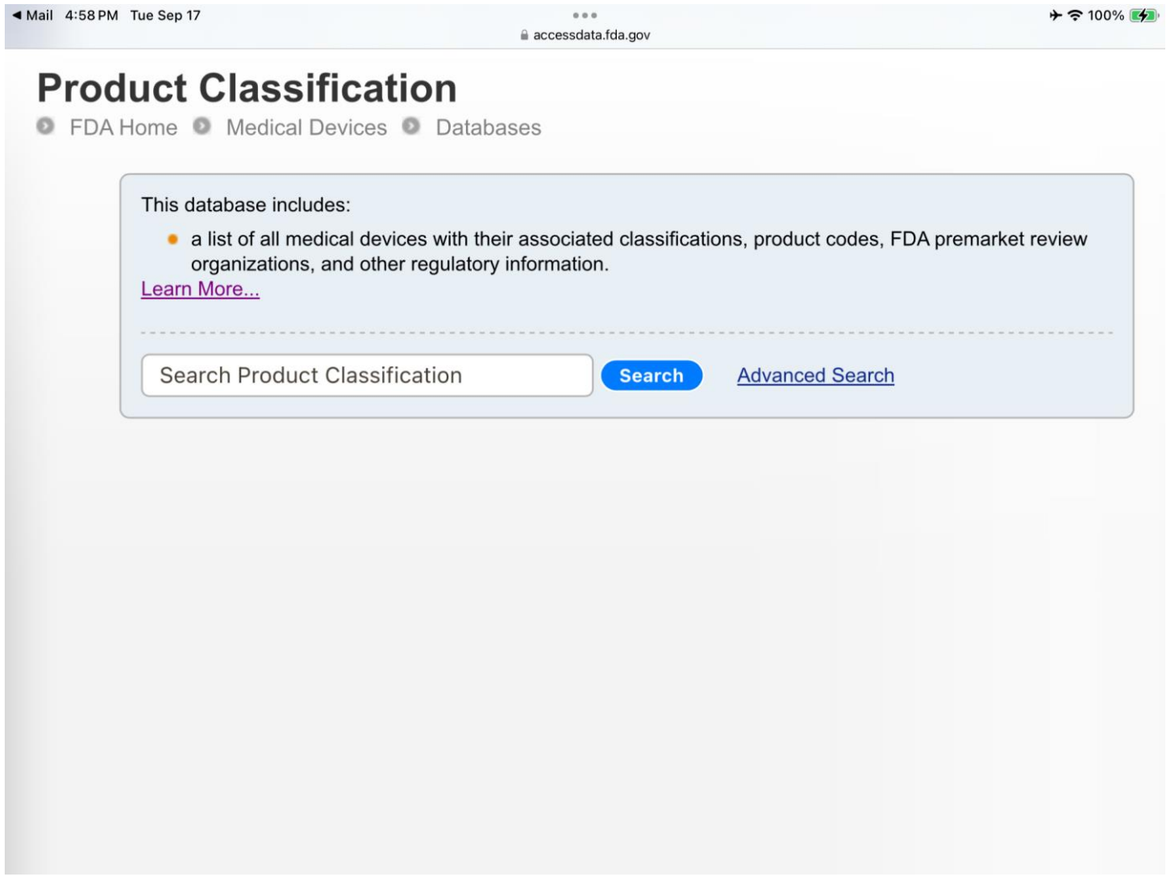
What is a product code?

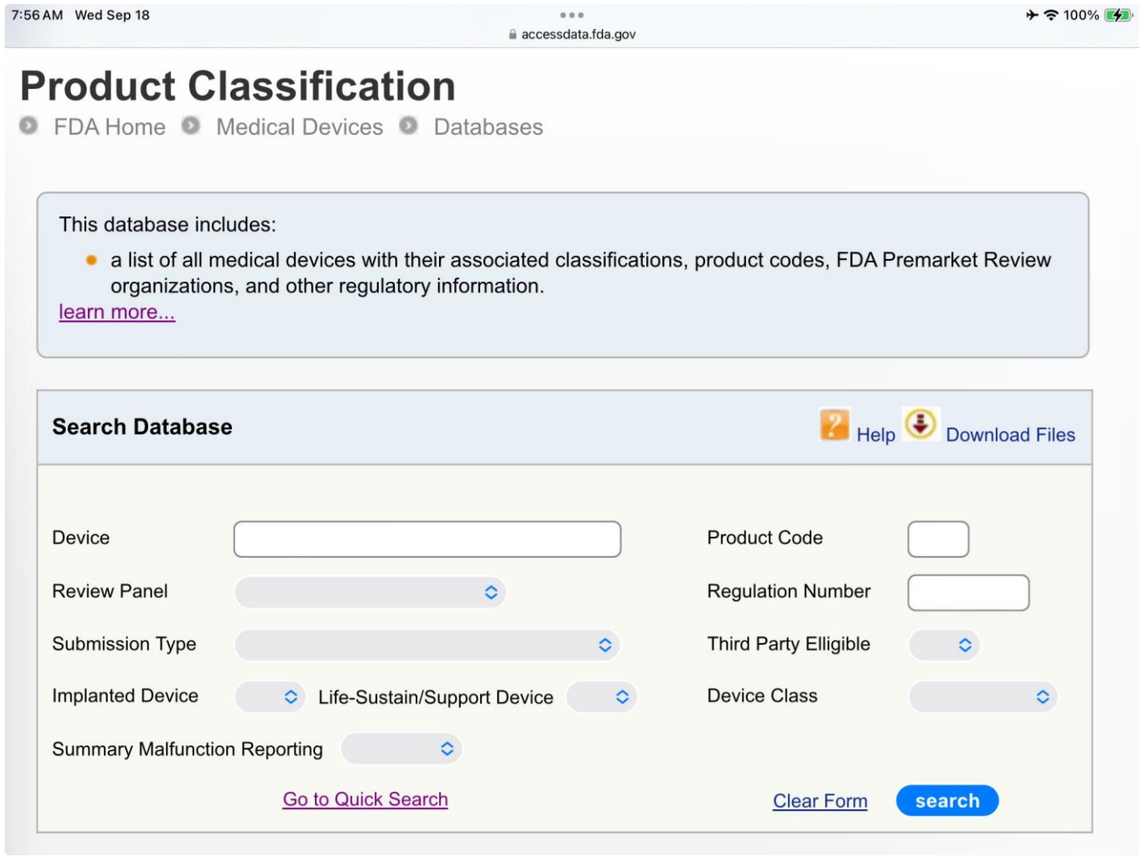
An FDA product code identifies the generic category of a test for FDA. A classification regulation may have multiple product codes associated with it. In this case, classification product codes help to delineate technology and indication subgroups within a regulation. However, a product code is only associated with one classification regulation or no regulation at all. In the latter case, they serve to categorize unclassified or Class III, PMA devices. Classification product codes are assigned and maintained by the FDA.

FDA product classification webpage

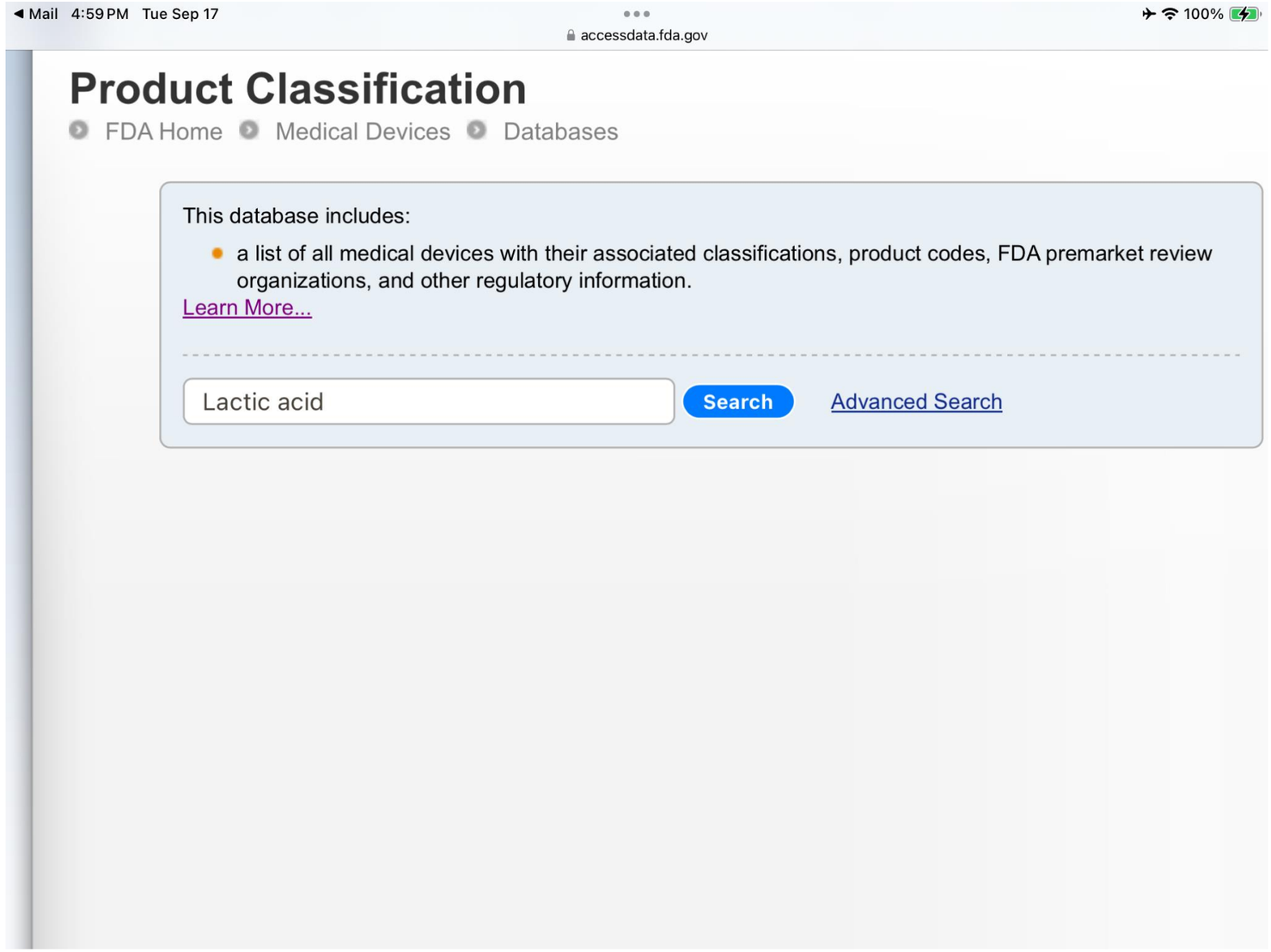


Search options – Simple or Advanced



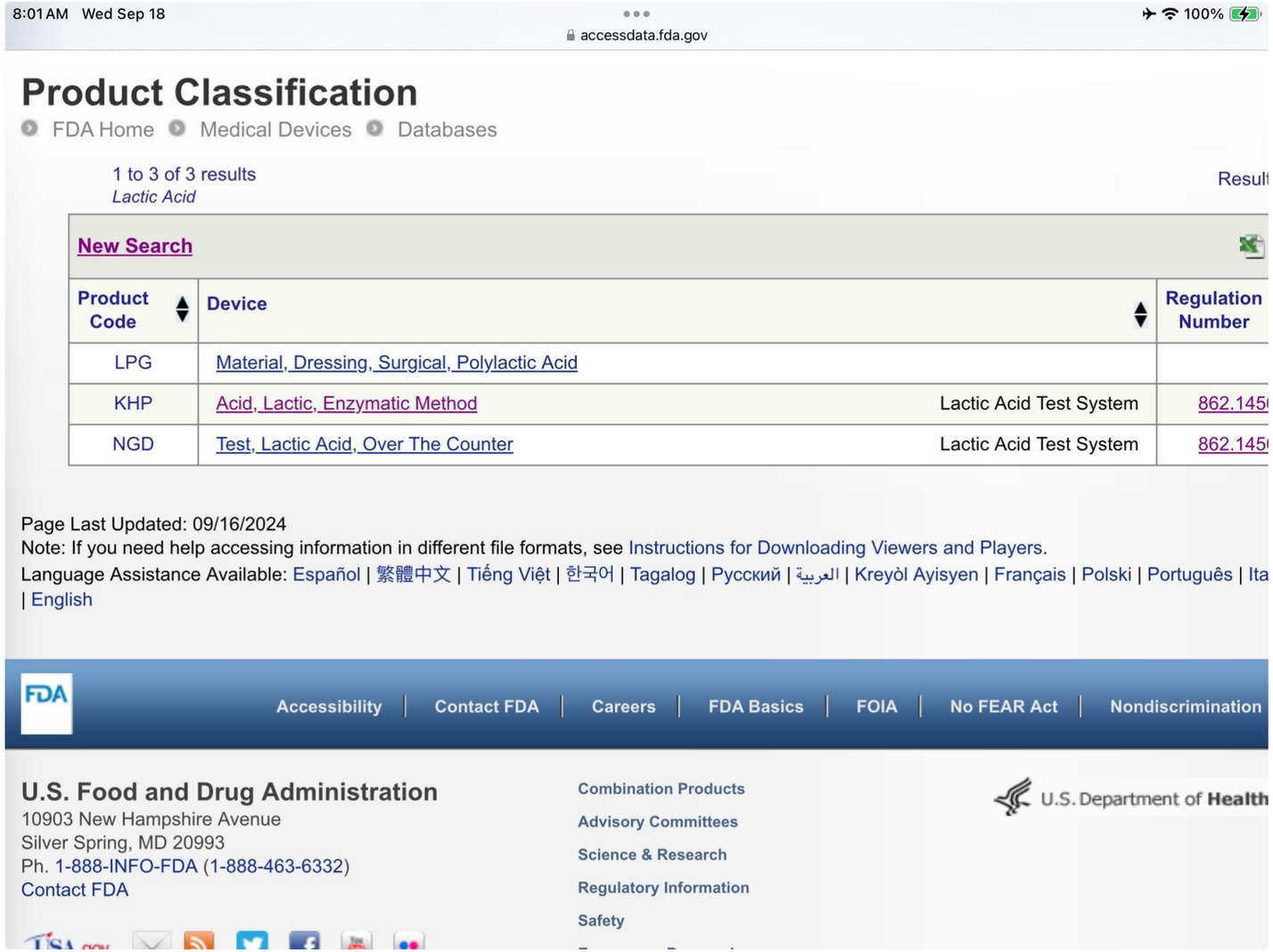


First Example – Lactic Acid – Class I Exempt

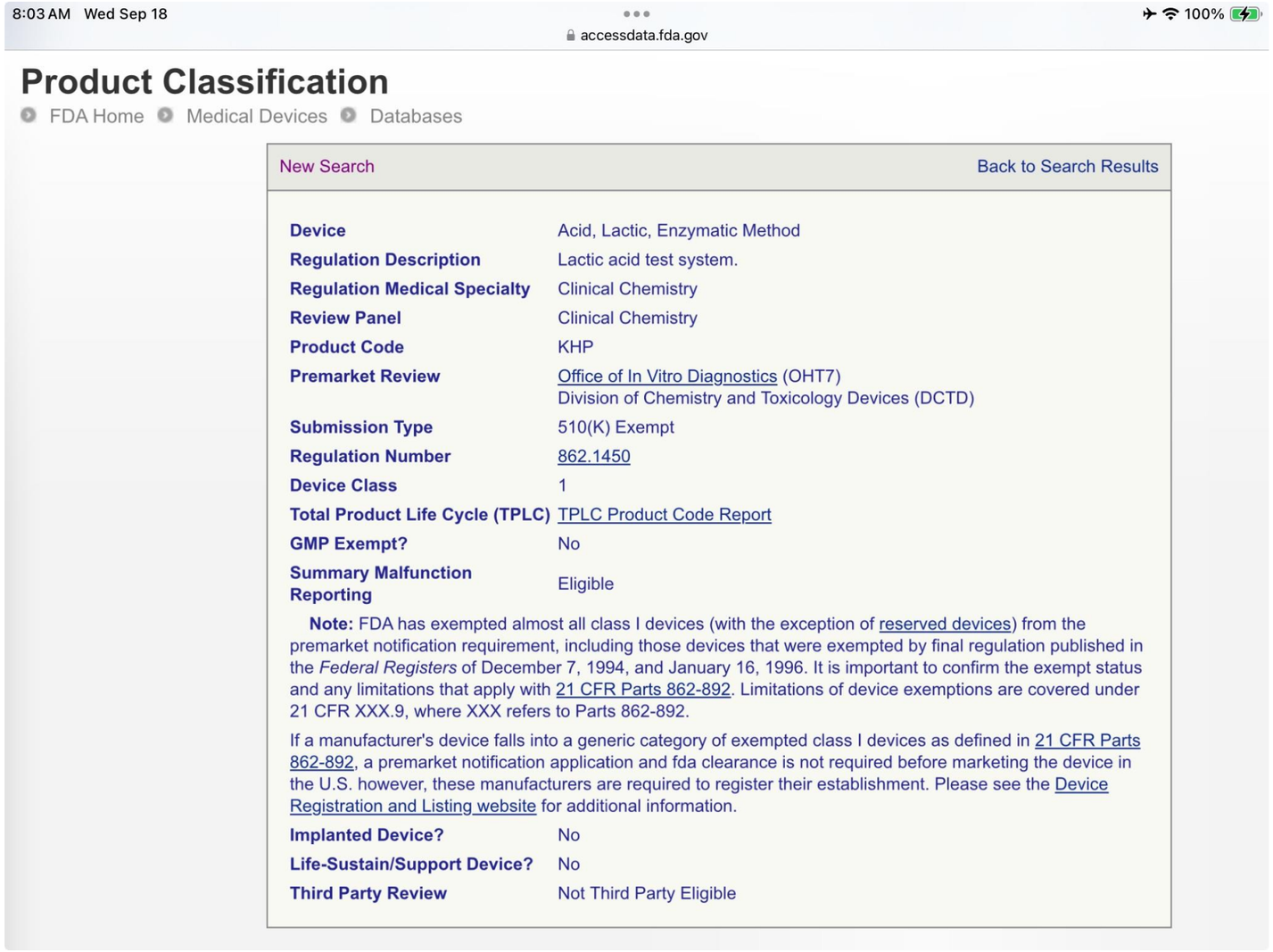


Lactic Acid

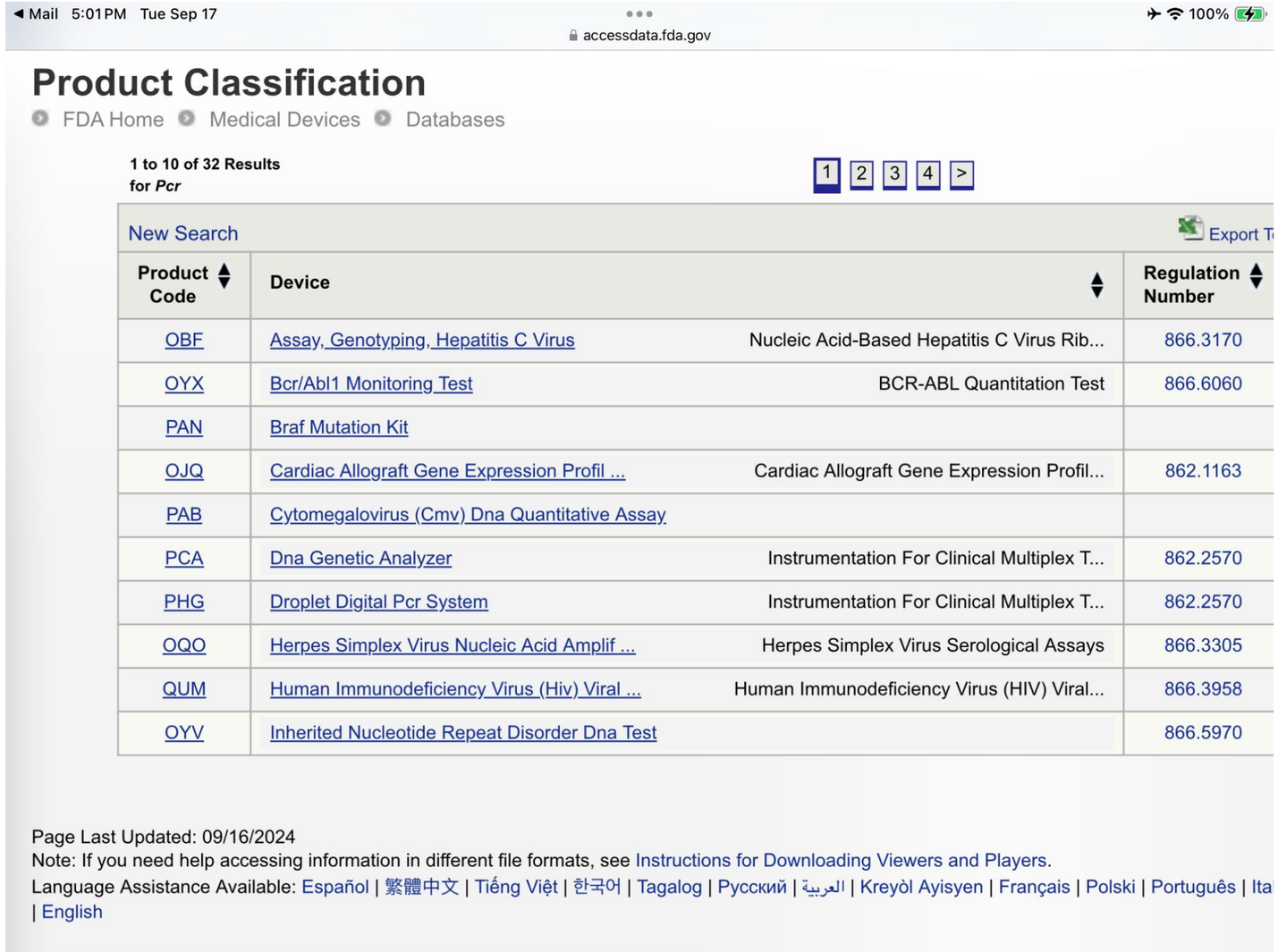
First page



Lactic Acid – Enzymatic Method



PCR – Class II Example



Product Classification

FDA Home › Medical Devices › Databases

1 to 10 of 32 Results
for *Pcr*

1 2 3 4 >

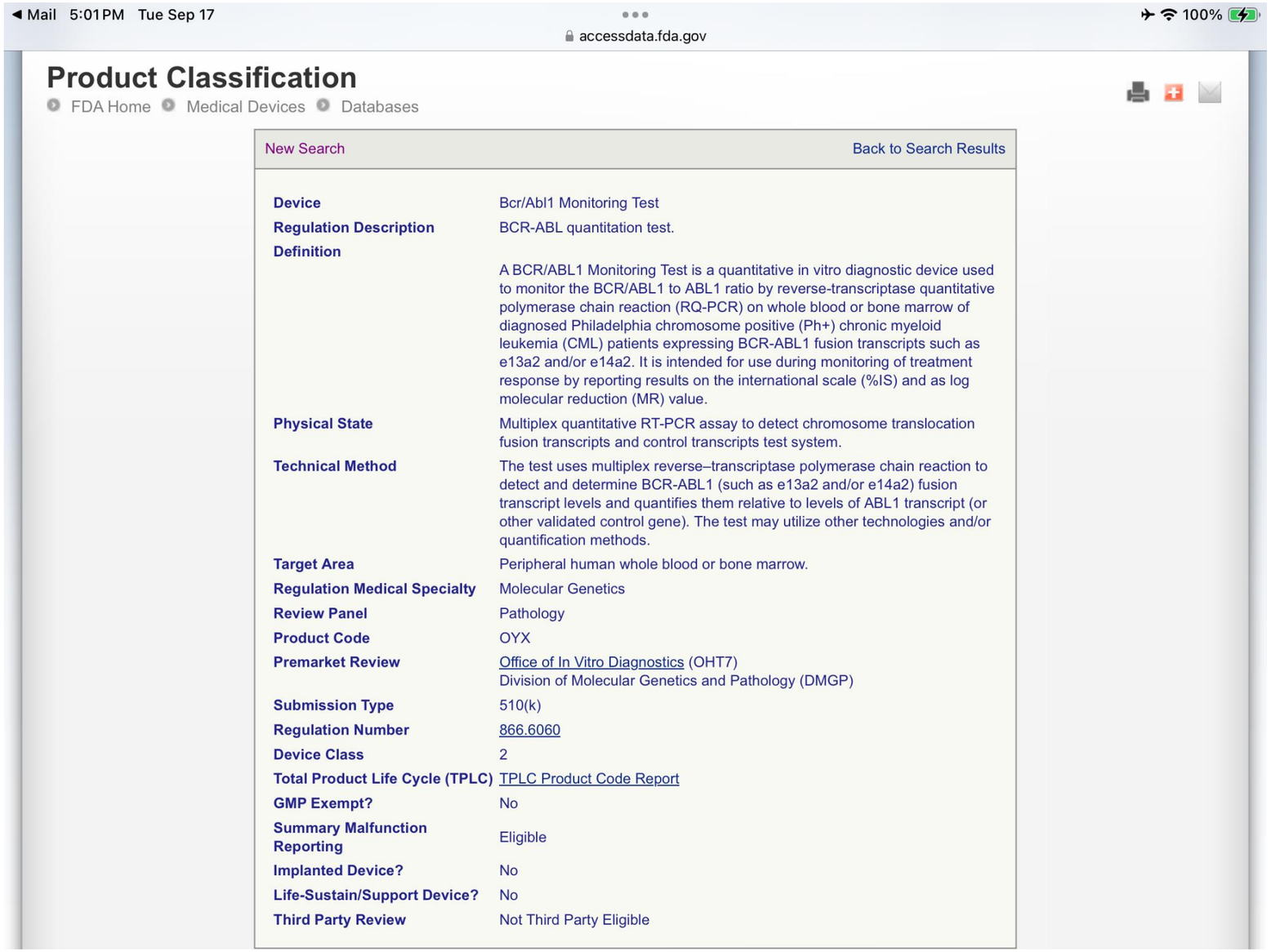
New Search

Export T

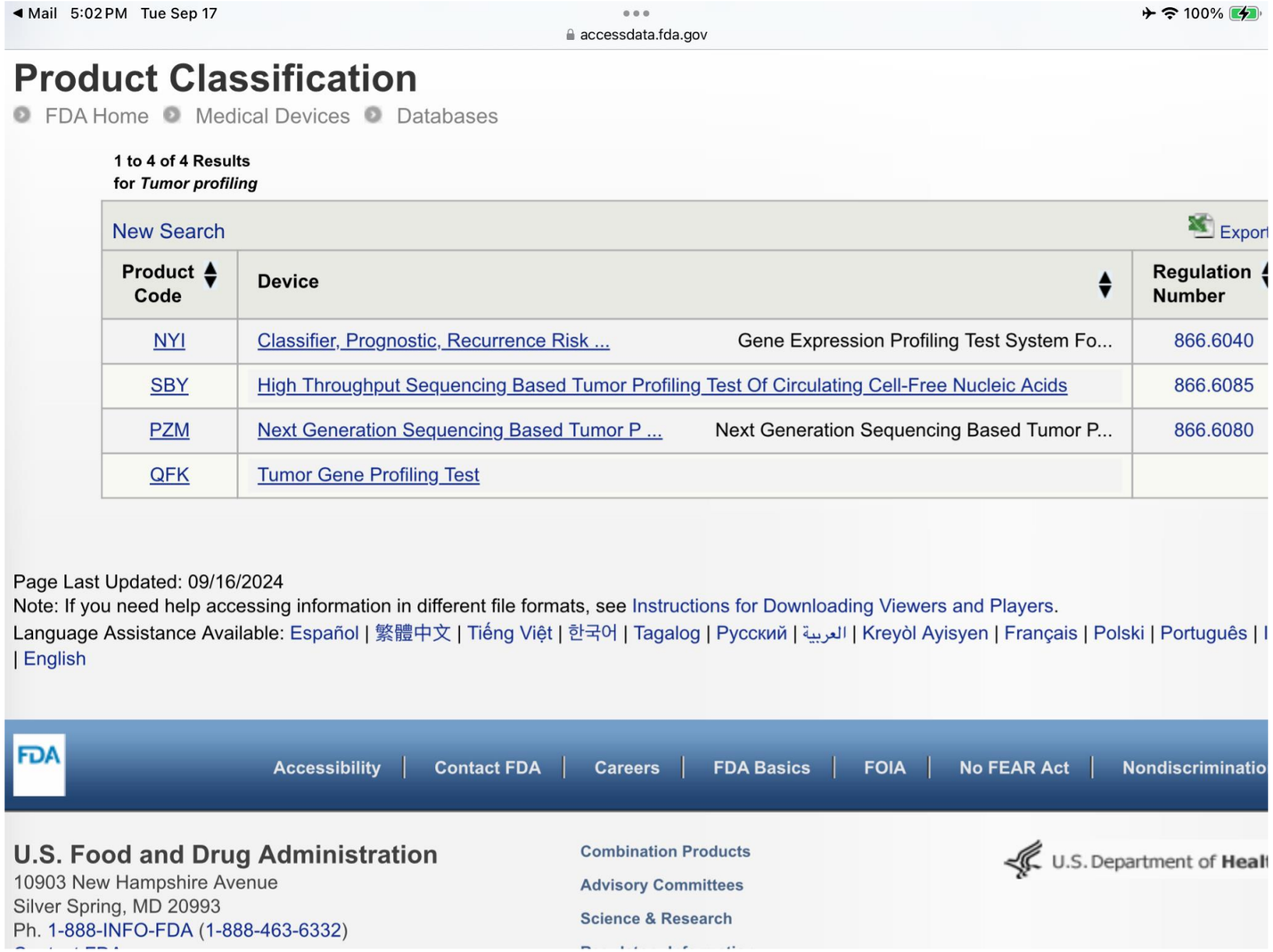
Product Code	Device		Regulation Number
OBF	Assay, Genotyping, Hepatitis C Virus	Nucleic Acid-Based Hepatitis C Virus Rib...	866.3170
OYX	Bcr/Abl1 Monitoring Test	BCR-ABL Quantitation Test	866.6060
PAN	Braf Mutation Kit		
OJQ	Cardiac Allograft Gene Expression Profil ...	Cardiac Allograft Gene Expression Profil...	862.1163
PAB	Cytomegalovirus (Cmv) Dna Quantitative Assay		
PCA	Dna Genetic Analyzer	Instrumentation For Clinical Multiplex T...	862.2570
PHG	Droplet Digital Pcr System	Instrumentation For Clinical Multiplex T...	862.2570
OQO	Herpes Simplex Virus Nucleic Acid Amplif ...	Herpes Simplex Virus Serological Assays	866.3305
QUM	Human Immunodeficiency Virus (Hiv) Viral ...	Human Immunodeficiency Virus (HIV) Viral...	866.3958
OYV	Inherited Nucleotide Repeat Disorder Dna Test		866.5970

Page Last Updated: 09/16/2024
Note: If you need help accessing information in different file formats, see Instructions for Downloading Viewers and Players.
Language Assistance Available: Español | 繁體中文 | Tiếng Việt | 한국어 | Tagalog | Русский | العربية | Kreyòl Ayisyen | Français | Polski | Português | Ita
| English

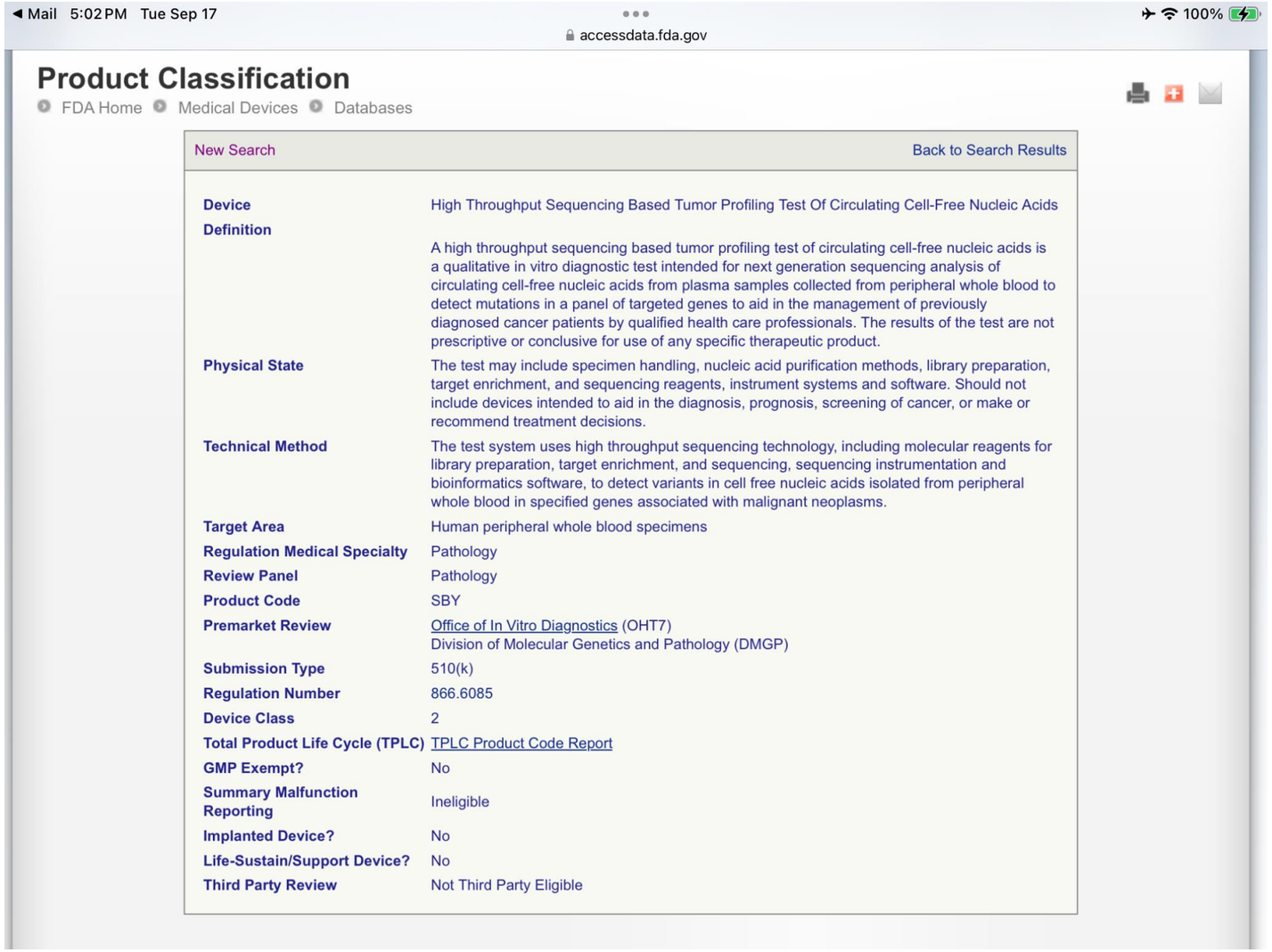
BCR-ABL Monitoring



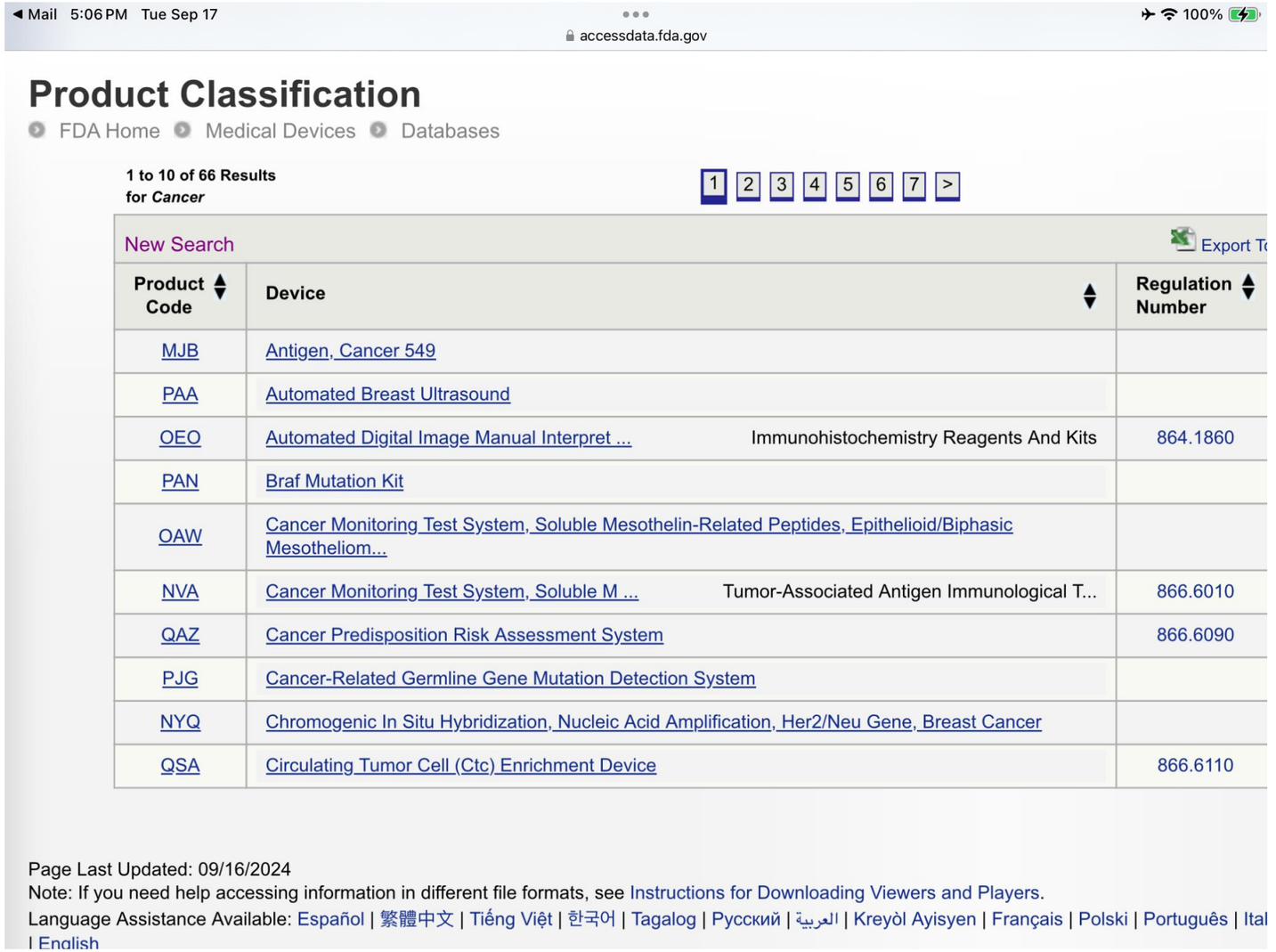
Tumor Profiling – Class II



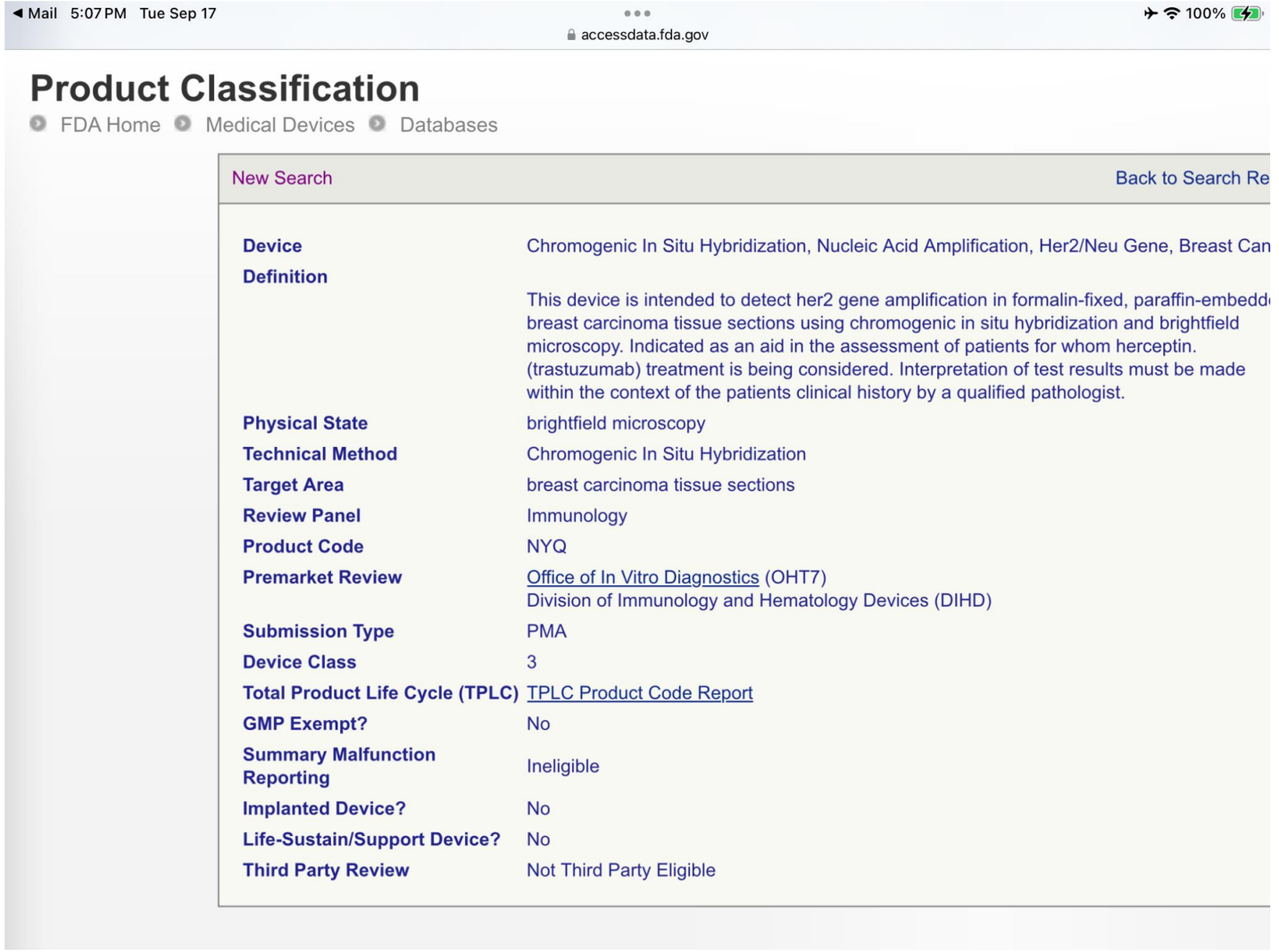
Tumor Profiling Example



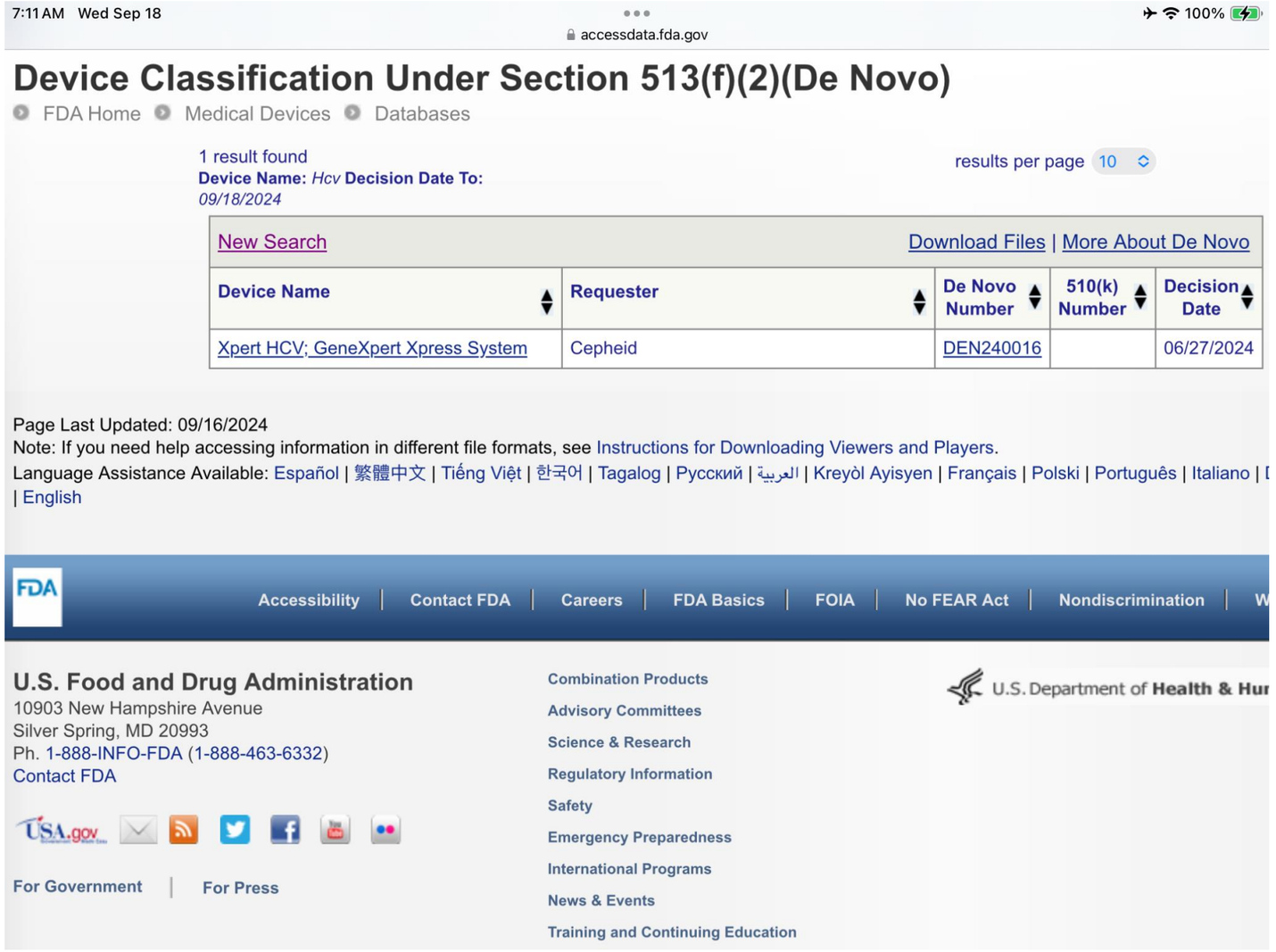
Cancer search – Class III



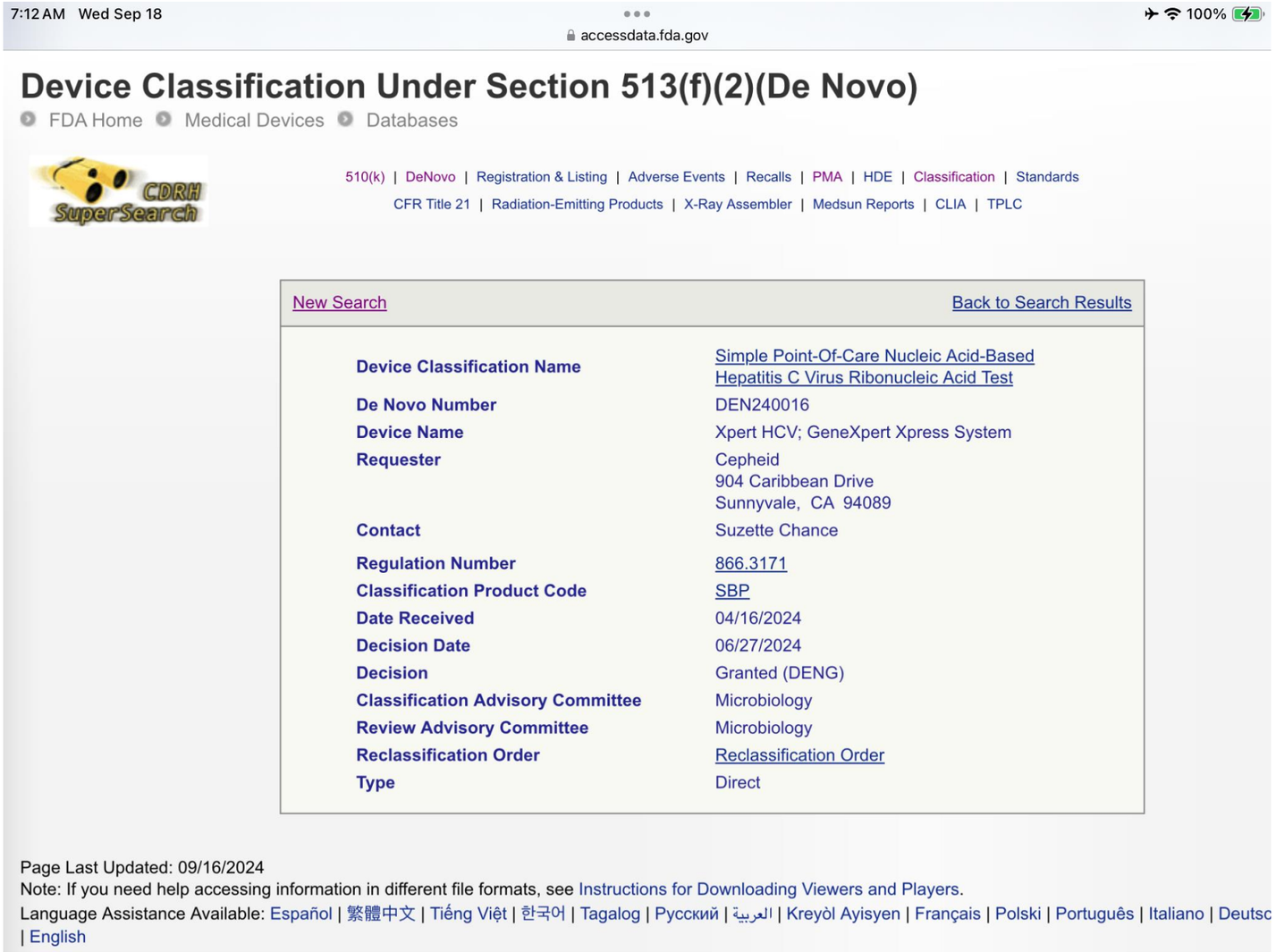
Class III – Her2/Neu



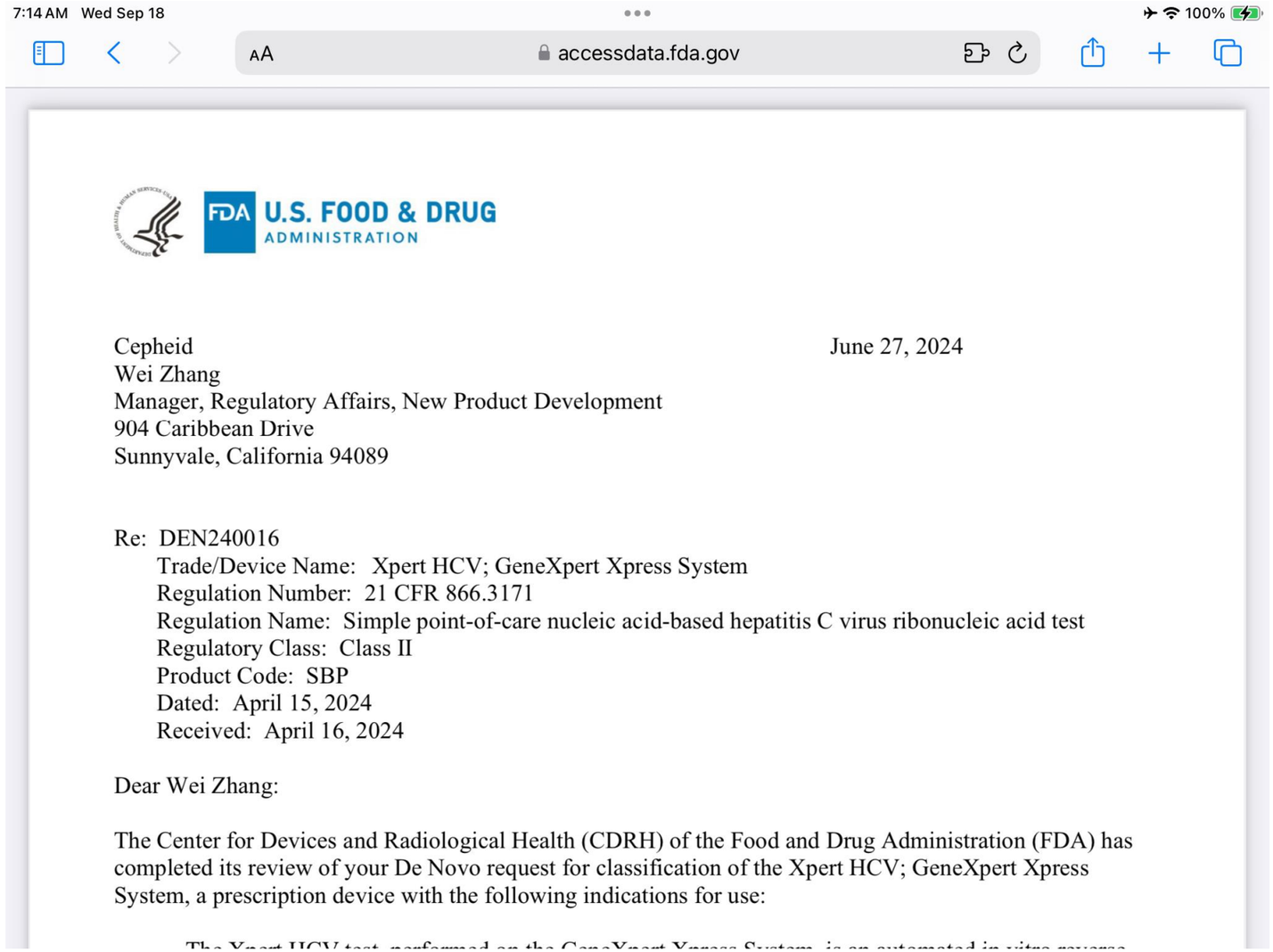
De Novo Database Search - HCV



De Novo Search - HCV



HCV De Novo – Additional Information



De Novo HCV – Special Controls

In combination with the general controls of the FD&C Act, the simple point-of-care nucleic acid-based HCV RNA test is subject to the following special controls:

(1) Any sample collection device used must be FDA-cleared, -approved, or -classified as 510(k) exempt (standalone or as part of a test system) for the collection of the sample types with which this device is intended to be used; alternatively, the sample collection device must be cleared in a premarket submission as a part of this device.

(2) The labeling required under 21 CFR 809.10(b) must include:

- (i) A prominent statement that the test is not intended for use as a donor screening test for the presence of HCV RNA from human cells, tissues, and cellular and tissue-based products;
- (ii) A detailed explanation of the principles of operation and procedures for performing the assay;
- (iii) Detailed descriptions of the performance characteristics of the device for each specimen type identified in the intended use based on the required analytical and clinical studies;
- (iv) A brief reference sheet (Quick Reference Instructions) for the intended user(s) that includes the name and intended use of the test, step-by-step instructions of all control and sample testing procedures for the identified specimen types, the result(s) interpretation recommendations, warnings and limitation statements, and information for troubleshooting or technical assistance with the device; and
- (v) Limitations, which must be updated to reflect current clinical practice and disease presentation and management. These limitations must include statements that indicate:
  - (A) The specimen types for which the device has been cleared and that use of this test kit with specimen types other than those specifically cleared for this device may result in inaccurate test results.
  - (B) When applicable, that assay performance characteristics have not been established in

Some thoughts when communicating with the FDA

The FDA staff are bright, hardworking, dedicated and want to be helpful to developers. They are prepared to be disrespected, as they too often are. Just like anything else, honey may be more effective in the long run than vinegar as it allows for free-flowing two-way problem-solving communication. If a developer asks for help they are usually more than willing to help.

They will use legal/regulatory language as their work must be ready to hold up in court, if needed. You might be surprised how often the FDA is threatened with legal action, even outside of LDTs.

They approach things from a scientific basis. New technologies are examined from this perspective, and they are sure to benefit from a brief primer on your technology.

New technologies may require different FDA approaches, always feel free to suggest approaches that may work.

Links

FDA Webinar - In Vitro Diagnostic Product (IVD): Classification Webinar - In Vitro Diagnostic Product (IVD): Classification - 07/16/2024 | FDA

Product Classification Database https://www.fda.gov/medical-devices/classify-your-medical-device/product-code-classification-database

PMA Class III Database https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMA/pma.cfm

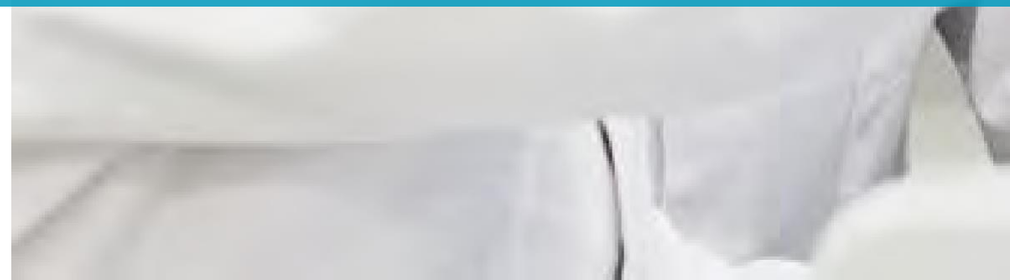
De Novo Database (typically Class II) - https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMN/denovo.cfm

510(k) Database (Class I, Class II and/or Exempt) https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMN/pmn.cfm

De Novo Classification Process https://www.fda.gov/media/72674/download

Q-Submission https://www.fda.gov/media/114034/download

Questions and Answers



Top 5 Takeaways

- FDA classifies medical devices based on risk and intended use of the device.
  - CLIA has its own separate system for categorizing test complexity. Risk does not equate to complexity.
- Factors to consider to determine if your LDTs is Class I, II or III are **intended use** and **risk posed to patients**.
- The risk and intended use also determines the extent of regulatory controls.
- The FDA recommends searching the medical device database for examples to help determine the appropriate regulatory controls for IVDs.
- Device determination and pre-submission requests are available to assist with classification and regulatory pathway questions.

Six-Part Webinar Series on LDTs

- Register for our other webinar programs:

  Understand and Prepare for the Impact of the FDA's LDT Final Rule

  - How You Meet Stage 1's Adverse Event Reporting Requirement (November 7, 2024)
  - Stage 1 Basics on Corrective Action and Removal Reporting (January 9, 2025)
  - The Stage 1 Rules on Quality Systems Complaints (March 20, 2025)
  - How Enforcement Discretion Categories & Modification Rules Apply to Your LDTs (May 8, 2025)
  - Navigating FDA LDT Oversight Requirements During Public Health Emergencies (July 10, 2025)

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