This information should not be considered to represent advice or guidance on behalf of the U.S. Department of Health and Human Services or any agency or office thereof.

Regulatory Knowledge Guide for In Vitro Diagnostics

NIH SEED Innovator Support Team

Introduction

An estimated 3.3 billion ***in vitro* diagnostic** (IVD) tests are performed in the U.S. every year.[1] They range from reagent devices such as urine dip-and-read sticks, to glucose monitors, to sophisticated genetic tests that are used to predict response to cancer therapies. They can encompass reagents, instruments, or other systems and are used to diagnose a disease or to monitor and treat health conditions.

IVDs are medical devices regulated by the U.S. Food and Drug Administration (FDA). Within FDA, the Center for Devices and Radiological Health (CDRH) and, for a subset of medical devices the Center for Biologics Evaluation and Research (CBER) are responsible for ensuring the safety and effectiveness of IVDs. The FDA lists all IVDs cleared or approved since November of 2003 in a searchable database.

The term *in vitro* refers to processes that take place in a controlled environment outside of a living organism. An IVD is intended to be used for the collection, preparation, and examination of specimens taken from the human body. Such specimens can include tissue, blood, urine, saliva, and other bodily fluids. Non-IVD devices function primarily in or on an individual, whereas an IVD involves the collection or examination of human specimens that have been removed from the body.

The FDA's regulations on IVDs, like those for other medical devices, are intentionally flexible and are used to regulate the safe and effective use of a broad range of products. While most IVDs are regulated by CDRH, some (e.g., those used to screen blood to assess blood donor and recipient suitability) are regulated by CBER. For example, CBER is responsible for pre-transfusion screening tests for the detection of infectious diseases, as well as reagents used for blood grouping, organ donation, antibody

[11] The Role of Lab-Developed Tests in the In Vitro Diagnostics Market | The Pew Charitable Trusts (pewtrusts.org)

detection, etc. This guide primarily focuses on IVDs regulated by CDRH. FDA provides more information on biological devices regulated under CBER.

FDA also has special rules that apply to certain IVDs that are beyond the scope of this guide. Those IVDs include laboratory developed tests (LDTs) and analyte specific reagents (ASRs). The LDT Regulatory Knowledge Guide provides more specific resources on laboratory testing and how to determine if a test is an LDT or IVD. Information about ASRs, are also not covered in this guide. Companion diagnostics (CDx) are IVDs that FDA has determined to be essential to the safe and effective use of a corresponding drug or biologic. More information on CDx can be found here. Figure 1 shows the connection of IVDs, LDTs, and CDx to Medical Devices and the relationship between them.

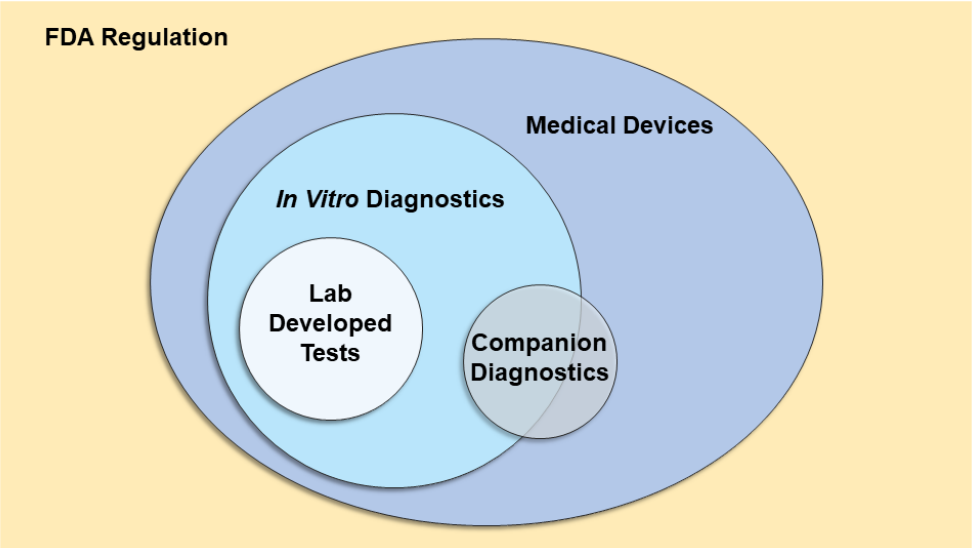


Figure 1. Landscape of medical device regulations focusing on diagnostic devices. Shades of blue (all but LDTs) indicate active regulatory authority of FDA (CDRH/CBER).

This Regulatory Knowledge Guide prepares innovators to develop and market an IVD. It is intended to complement FDA's regulatory guidance and identifies key points of consideration. It also highlights important distinctions between IVD and LDT development and Market Authorization processes.

Please use the Word navigation panel to jump to sections that are relevant for your specific needs. Bolded terms within the text are defined in the Glossary.

If you have questions about IVDs, please contact the SEED Innovator Support Team.

Key Takeaways

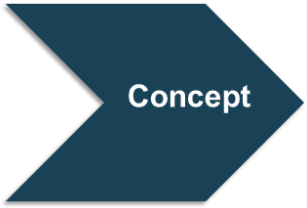
After reading this Regulatory Knowledge Guide, you will have a better understanding of how to develop and offer a test as an **IVD.** Specific topics that will be described include:

- Why IVDs are regulated as a medical device by FDA.
- Why, if you are proposing a new **intended use** for an IVD, you may need to get **De Novo** or **Premarket Approval** from CDRH.
- Why IVDs that rely on a proven technology may not need to conduct clinical studies since they may be able to show clinical validity by comparing analytical performance to a **predicate** device.

Table of Contents

List of Figures

List of Tables



1 Definition of an In Vitro Diagnostic (IVD)

IVDs are medical devices regulated by the U.S. Food and Drug Administration's (FDA's) Center for Devices and Radiological Health (CDRH) or the Center for Biologics Evaluation and Research (CBER)—depending on the intended use. However, there are several scenarios for which the standard FDA regulatory pathway may not apply. While this guide will focus on medical devices that FDA actively regulates, it is important to know that some IVDs may fall under FDA's enforcement discretion—which means that FDA's policy is to generally not enforce premarket review and other applicable FDA requirements.

Here are some examples of such scenarios where the standard FDA regulatory pathway may not apply:

- **Laboratory Developed Tests** (LDTs) are a type of IVD that is completely designed, manufactured, and used within a single laboratory. For many years, FDA has exercised "enforcement discretion" over LDTs. This means that FDA does not intend to enforce regulatory requirements for this specific type of device.

- Some IVDs that are currently under development and not approved for clinical diagnostic use are labeled for **Research Use Only** (RUO) **or Investigational Use Only** (IUO). These products are exempt from FDA premarket notification/approval requirements and some of the **Investigational Device Exemption** (IDE) regulations. However, there are certain requirements that must be met for RUO and IUO use and labeling. Labeling must be consistent with the manufacturer's intended use of the device.

- **Emergency Use Authorizations** (EUAs) are issued by FDA for unapproved devices or for unapproved uses of devices during a **public health emergency** when certain criteria are met, such as during the COVID-19 pandemic.

In all cases, you should be familiar with applicable FDA regulatory requirements before bringing an IVD to market.

1.1 Prototype Definition and Design

Before or alongside demonstrating the feasibility of a product, the idea for the technology needs to take form. Whether the device takes form on paper, in simulation, or as a prototype, consider how different versions of the proposed technology may have different regulatory consequences. Two IVDs with the same underlying materials and methods could have two different **intended uses** and/or **indications for use** statements. When defining what the product is and what it does, it is important to consider how it will be used and the corresponding regulatory implications.

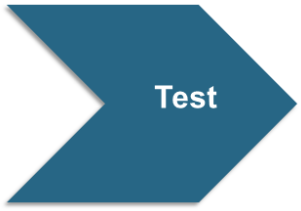
Even early on, it is helpful to consider potential regulatory pathways based on the intended use of the technology.

A prototype of the IVD is required before most feasibility testing can begin; confirmatory testing should be conducted on the final prototype. For example, sterility or biocompatibility testing (if applicable) is commonly performed on the "final finished form" of the device.

When designing your first prototype, you may be experimenting with different options for multiple components. Based on what you learn from these early prototypes, you will converge on a small set of options to be tested in a functional prototype. It is not uncommon to iteratively test component combinations and permutations in multiple prototypes before finalizing the IVD design.

1.2 Result Interpretation

The type of results that will be provided as the output of the IVD and how they are to be interpreted can determine the assay or procedure used to assess clinical validity, which is required as part of the regulatory process. Whether the output will be a positive or negative, a quantity, or more detailed information such as an index or score, it is important to define it early in the development process. Similarly, whether the output is used to make a screening or diagnostic decision impacts the performance thresholds when the prototype is validated. Output interpretation informs both the development of the prototype and serves as a focal point for FDA's review of the safety and efficacy of the IVD.



2 Feasibility Testing

If the technology is very early in its development, then a variety of active research may be ongoing simply to prove whether the idea is feasible. Such research—conducted without the use of or testing on humans or human samples, does not generally fall under FDA oversight. Note, however, that any research (related to feasibility or otherwise) that includes the use of or testing on humans or human samples generally falls under FDA oversight (in addition to Institutional Review Board (IRB) review). Figure 2 provides an overview of the significant testing steps in IVD product development.

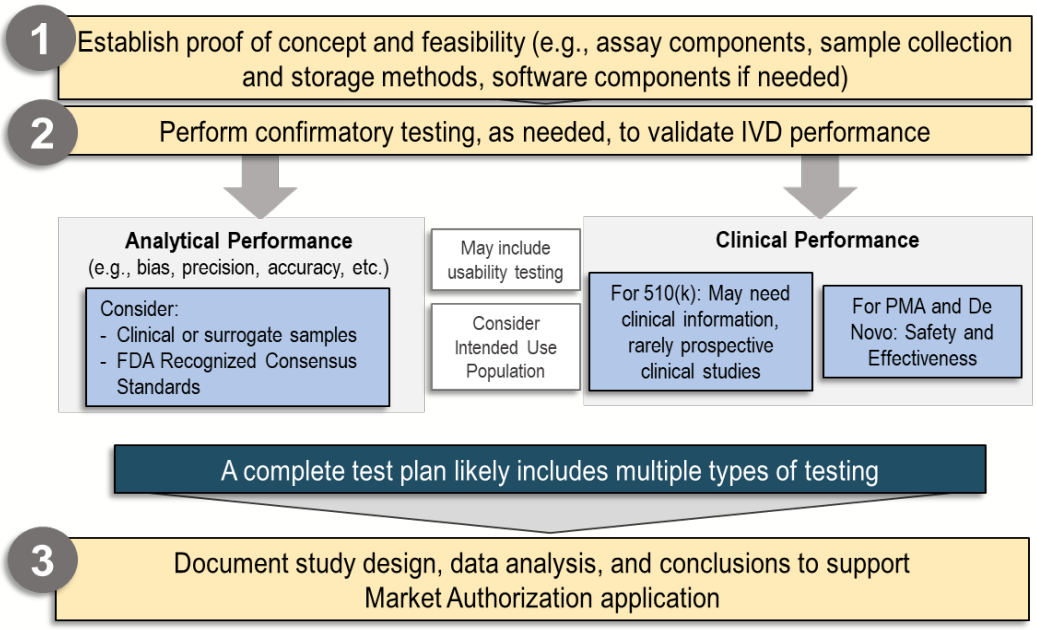


Figure 2. Product development and testing

2.1 Basic Test Performance Characteristics

It is important to establish basic performance characteristics early in the process, so later confirmatory testing can be planned based on the performance characteristics that will be used for the IVD. Basic characteristics to establish before confirmatory testing can include:

- **Accuracy**: The closeness of the measurement to the true value.
- **Precision**: The closeness of repeated measurements to one another.
- **Reportable range**: The range of analyte concentrations for which the test system can accurately report results.
- **Analytical sensitivity**: The assay's ability to detect very low concentrations of a given substance in a specimen. It is the number of true positive detections divided by the sum of the number of true positives and the number of false negatives.
- **Analytical specificity**: How well an assay detects a specific substance against background interference from other substances. It is the number of true negative detections divided by the sum of the number of true negatives and false positives.
- **Reference intervals**: The range of IVD output values that correspond to normal or healthy populations.

2.2 Sample Sources, Sample Collection, and Storage Methods

Sample collection and storage methods along with sample stability, are ideally determined before full validation testing. It is important to assess stability using the variables and conditions that will be encountered in real-world use of the IVD. Considerations should cover all predictable conditions that will be encountered between sample collection and testing, such as temperature (including freezing and thawing, as applicable), impact of light, potential evaporation of solvent, potential interaction with the storage or test vessel, etc.

Assessing test sample stability and storage may be part of the analytical studies for IVD validation, but it is best to establish sample storage and stability before validation testing since they may impact other test results.

Test specimens are needed to enable all phases of IVD development. Therefore, it is important to ensure you will have access to the type and amount of data and samples required to complete your feasibility (and validation) testing. You may want to find multiple sources of test specimens—repositories, hospital systems, CROs, etc.

If prospective human specimens are required for feasibility testing, consider the Early Feasibility Study IDE program, though the first point of contact for guidance will be the study's IRB. For additional information on early feasibility studies, please see Section 3.2 of the Regulatory Knowledge Guide for Therapeutic Devices.

2.3 Assay Component Definitions

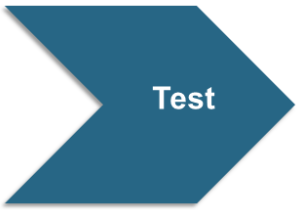
Feasibility testing relies on the clear identification and characterization of analytes, which are substances—such as proteins, chemical compounds like glucose or cholesterol, or DNA—that can be targeted with a certain **reagent**. Different analytes require different reagents. It is essential to have a detailed understanding of the materials and substances being used to demonstrate feasibility and optimize the diagnostic test.

It is also important to understand which methodology should be used to test the analyte. Examples of test methods include:

- Immunoassays
- Molecular Diagnostics
- Flow Cytometry

For instance, real-time polymerase chain reaction testing (a molecular diagnostic method) is used to identify mutations of the KRAS gene in cancer cells.

Resource:
FDA: Analyte Specific Reagents



3 Analytical Validation

Analytical validation is necessary to demonstrate the technical reliability of the IVD—that is, how well it measures the analyte. There are numerous methods for analytical validation of an IVD.

3.1 Quality Assurance and Predicate Comparisons

Testing the IVD for analytical validity is an opportunity to establish processes to ensure reagents, specimens, and other components are stored, transported, and used safely. For example, the IVD can be tested to characterize its performance under a variety of improper-use scenarios, and these tests can inform quality control processes that you are required to establish in the **quality management system** (see Section 8). The processes may also inform the indications for use and/or labeling of the IVD.

Another means of establishing analytical validation is through a **predicate** device comparison. If there is an existing predicate device, you can perform confirmatory testing by comparing your IVD's performance and specifications directly to that of the predicate. Demonstrating that the new diagnostic is the same or better in all capacities to the predicate is one way to support a claim of **substantial equivalence**. This is often cheaper and more direct than creating a new body of evidence and is a commonly used approach for supporting a 510(k) market application.

Resources:
NIH SEED: 510(k) Documentation and Application
NIH SEED: 510(k) Pre-Submission Meetings
NIH SEED: Quality Management Systems for Medical Devices

3.2 Validating Performance

A wide range of differences in materials, conditions, and measurements can lead to changes in performance of an IVD. Identifying factors that could impact the accuracy and clinical reliability of the IVD is critical to the analytical validation process. When designing validation studies, you should identify:

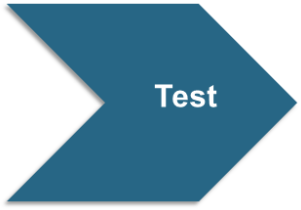
- Factors of uncertainty: Part of a validation plan is to identify all factors that could impact diagnostic performance (i.e., factors of uncertainty) and to account for as many of them as possible. Not all variations may be testable, but their potential risks can be mitigated in other ways, such as labeling or **indications for use**.
- Limitations of measurement: Metrics used in typical analytical validation plans include reference interval, **limit of detectability**, analytical sensitivity/specificity, and **linearity**. After identifying which are applicable to the IVD, the goal is to determine the optimal operating thresholds for the IVD, as well as the upper and lower limits for those thresholds.
- **Accuracy** and **precision**: Part of most IVD analytical test plans is a study to determine the accuracy and precision of the measurement. Accuracy is demonstrated by comparing the IVD to a valid scientific reference for the quantity measured. It measures the amount of bias in the IVD. Precision is

demonstrated by repeating measurements in similar and in different configurations. It measures the repeatability and reproducibility of the IVD.

3.3 Next Generation Sequencing (NGS) and Inherited Diseases

NGS is a type of high-throughput sequencing either of the entire human genome or of subsets of genes or areas on a gene. As this type of IVD is specific to the field of genetics, the analytical validation requirements (may) differ from other IVDs. Currently, comprehensive **standards** for analytical validation applicable to NGS-based tests do not exist. FDA published this guidance document including considerations for designing, developing, and analytically validating NGS IVDs.

Resources:
FDA: The Special 510(k) Program
FDA: Recognized Consensus Standards
FDA: Considerations for Design, Development, and Analytical Validation of Next Generation Sequencing (NGS)–Based In Vitro Diagnostics (IVDs) Intended to Aid in the Diagnosis of Suspected Germline Diseases



4 Clinical Validation

Clinical validity of an IVD implies the measurements of the IVD device (test) are capable of reliably identifying, measuring, monitoring, or predicting the presence or absence of a clinically defined condition, disorder, or health status of interest in a clearly defined target population. The testing required to show clinical validity depends on the type of device and its **intended use**.

Testing for clinical validity does not always constitute a clinical trial, primarily when it does not involve prospective participation from patients. The NIH has prepared a list of example case studies that can be a helpful reference when determining whether a research activity constitutes a clinical trial; for IVDs, see especially cases 7a and 7b.

4.1 Intended Use and Predicate Devices

IVDs that use a well-characterized technology with an intended use that has been classified into Class I or Class II may be able to utilize the 510(k) pathway. In many instances, studies comparing analytical performance of a new IVD to a predicate device using clinical samples are often sufficient to demonstrate clinical validity. For example, high blood calcium levels are linked to parathyroid disease, and therefore a test's analytical accuracy on such clinical samples may be all that is required to show clinical validity. Confirm with FDA if this type of study plan is appropriate for your IVD.

IVDs that rely on proven technology may not need to conduct clinical studies, they may be able to show clinical validity through analytical performance compared to a predicate device.

Resource:
FDA: The 510(k) Program: Evaluating Substantial Equivalence in Premarket Notifications
NIH SEED: Mapping Your Way Through the FDA's 510(k)

4.2 New Technologies

When an IVD uses a novel or unproven technology, a prospective clinical study may be needed to show clinical validity, safety, and effectiveness. Safety and effectiveness are measured by either appropriate clinical endpoints, diagnostic performance, or both. If an IVD requires a clinical study, the pivotal evaluation is usually not a clinical outcome study but rather, is a diagnostic clinical performance study. For example, the ability of a human papillomavirus test to predict cervical cancer (target condition) may be assessed in a clinical performance study. Clinical outcome studies are generally needed if the diagnostic device result is used during a treatment or management intervention. Device performance is assessed in part by the intervention's effect on a subject's outcome. Clinical outcome studies may be appropriate if, for example, clinical benefit (improvement in a clinical outcome) from accurate diagnosis is not clear.

Resources:
FDA: Design Considerations for Pivotal Clinical Investigations for Medical Devices
MDIC: A Framework for Developing Credible Evidence of Analytical Validity, Clinical Validity, and Clinical Utility for IVDs

4.3 Clinical Validation Metrics and Assay Selection for Validation

Clinical validity metrics show how well the test measures or predicts the clinically defined health status of interest. Clinical validity metrics may include, but are not limited to:

- Clinical sensitivity: The percentage of individuals with the target condition who will have positive test results (i.e., the ability of a test to detect a true positive)
- Clinical specificity: The percentage of individuals who do not have the target condition who will have negative test results (i.e., the ability of the test to detect a true negative)
- Predictive values: The proportion of individuals in the **intended use** population who have or do not have the target condition and receive a positive or negative result respectively (determined by the test's sensitivity and specificity and the prevalence of the condition for which it is used)

The **assay** or procedure used to assess clinical validity is generally based on the type and interpretation of results that will be provided as the output of the IVD to physicians/patients. These include:

- Quantitative assays that provide information about the amount of analyte in the sample
- Semi-quantitative assays that provide ordinal numerical values
- Titer assays that report the relative amount of an analyte
- Multi-analyte assays with algorithmic analyses

4.4 Use of Certified Testing Lab and/or FDA Recognized Consensus Standards

For IVDs, there are standards corresponding to a wide range of validation methods and metrics, such as CLSI EP07 on Interference Testing or CLSI EP17A on Limits of Detection. All FDA recognized consensus standards are available online, and their view can be filtered (for example, ones that pertain to IVDs). Standards that are recognized by FDA provide sufficient test methods to demonstrate safety and efficacy of the technology within the context of that standard.

Some standards include tests that are readily (and likely best) performed by certified testing labs. If you cannot demonstrate, for example, the electromagnetic compatibility in-house (most cannot), then you can send your device to a test lab.

Resource:
FDA: Recognized Consensus Standards

4.5 Aligning Test Data with Intended Use Populations

While it is not required that initial development testing data represent the entire intended use population, FDA will likely ask you to justify how your clinical validation testing is appropriate and applicable for the intended use population.

The innovator should be able to explain how the population tested is relatable to the intended use population.

For example, if testing was done in people under 65, but the test is intended for people over 65 as well, applicability to the over-65 population should be justified. Determining the intended use population is also an important factor for coverage determinations and reimbursement, especially by government payors.

4.6 Artificial Intelligence/Machine Learning (AI/ML)

The AI/ML algorithms that support digital health technologies may have many variations, options, and parameters. It is important that the underlying algorithm does not change during or after the human testing phase—because the supporting validation must reflect the version of the device that will be on the market. The algorithm should be essentially finalized and documented before large-scale human testing.

For a more complete discussion on updating AI/ML algorithms, please refer to Section 6.1 of the Regulatory Knowledge Guide for Digital Health.

5 FDA Market Authorization Preparations

There are several significant milestones you should complete prior to submitting your IVD for Market Authorization.

5.1 Pre-Submission Meetings with FDA

Carefully consider when the time is right to request a **pre-submission meeting** with FDA. These meetings may focus on questions about the clinical study protocol or data challenges, and/or the regulatory approach that is going to be taken to obtain feedback. Pre-submission meetings are confidential, interactive, have a relatively quick turnaround, and are free. Pre-submission meetings are typically scheduled 60-90 days after the request is submitted, allowing manufacturers to factor this time span into their planned development activities. It is highly recommended to meet with FDA before applying for Market Authorization.

Pre-submission meetings with FDA provide the opportunity to get feedback and advice before submitting an IDE or marketing application.

To get the most out of the meeting, prepare a short list of relevant questions (five or less) related to one topic. Include a description of the device, its **intended use**, a summary of any previous discussions, and a brief description of product development.

For a more complete set of guidelines regarding meetings with FDA, see Section 4 of the Regulatory Knowledge Guide for Therapeutic Devices.

Resource:
FDA: Requests for Feedback and Meetings for Medical Device Submissions: The Q-Submission Program
NIH SEED: Strategies for Communicating Effectively in Writing with CDRH

5.2 Safety and Efficacy or Substantial Equivalence

The test plan (and its results/conclusions) is one of the most substantial parts of a marketing application to FDA. The data gathered supports the statements about what the device can do and how well it performs. Some studies involve clinical data and others do not, but nearly all innovative medical devices require proof of their function.

For more information on substantial equivalence, please refer to Section 5.3 of the Regulatory Knowledge Guide for Therapeutic Devices.

5.3 Expert Guidance and Regulatory Affairs Consultants

Though FDA and NIH provide many resources to navigate the regulatory process, it is still a complex and time-consuming task, and having an experienced regulatory professional lead this effort is important. Most device companies (even mature ones) have under 10 employees and therefore use external support to submit information to FDA. If you do not have a regulatory expert on staff, it is important to engage a respected and appropriately qualified external team with diverse subject matter expertise to support your regulatory filing. Partners may include a larger medical device company, or a company with a similar product on the market. Regulatory affairs consultants are often part of small firms or organizations that specialize in a specific product area.

For more information on industry partners and regulatory affairs consultants, please refer to Section 5.2 of the Regulatory Knowledge Guide for Therapeutic Devices.

5.4 Humanitarian Device Exemption (HDE)

Devices that are developed to address diseases and conditions that affect 8,000 or fewer patients per year nationwide may obtain **humanitarian use device** (HUD) status from FDA. For such populations with rare conditions, limited clinical evidence can be collected due to limited access and smaller sizes of the patient population, as well as the lack of available comparable devices. HUD status may be an option for select IVD innovators. The marketing application for such devices is called an HDE. HUDs do not have a predicate device with the same intended use.

While an HDE application is similar to a **Premarket Approval** (PMA) application, the HDE application is exempt from the effectiveness requirements entailed in a PMA. This means that, at a minimum, safety and probable benefit must be demonstrated. Approval is given when the benefit outweighs the risk—as is the case with EUAs. While this is a lower regulatory hurdle to overcome compared to the PMA process, other considerations (such as reimbursement restrictions) should be evaluated when determining whether an HDE is appropriate.

Resources:
FDA: Humanitarian Use Device (HUD) Designation
FDA: Getting a Humanitarian Use Device to Market
NIH SEED: Humanitarian Use Devices

5.5 Dual 510(k) Submission and CLIA Waivers

Tests that either are waived by regulation under 42 Code of Federal Regulations (CFR) 493.15(c) or are approved for home or **over-the-counter** (OTC) use are automatically categorized as **Clinical Laboratory Improvement Amendment** (CLIA) waived by FDA.

If a test would not automatically be categorized as CLIA waived but is simple to use, with a low risk of inaccurate results, and is used at the **point-of-care** (which often requires CLIA waived categorization) a dual submission can be considered. This optional pathway allows submission of both a **CLIA Waiver by**

Application (for an otherwise "moderate complexity" test) and a 510(k) premarket notification to FDA at the same time. Traditionally, FDA determines CLIA complexity categorizations post-market approval. The dual submission pathway provides an opportunity to simplify and speed up the process by combining the 510(k) and CLIA Waiver by Application pathways. This requires foresight and up-front planning.

While the dual submission pathway can speed up the review process, FDA requests that the same information and level of detail is submitted as would be for separate 510(k) and CLIA Waiver applications. Some comparison and reproducibility study data may be submitted in a single set.

Figure 3 is an overview of FDA's Medical Device User Fee Amendments (MDUFA) IV decision timeframes.

Type of Application	Review Time
510(k)	90 FDA days

Type of Application	Without Panel Review	With Panel Review
Dual 510(k) and CLIA Waiver	180 FDA days	320 FDA days
CLIA Waiver [only]	150 FDA days	320 FDA days

Figure 3. FDA's Medical Device User Fee Amendments (MDUFA) IV decision performance goals and review timeframes by application type

Note: FDA days are calculated as the number of calendar days between the date the 510(k) was received and the date of a MDUFA decision, excluding the days the submission was on hold for a request for additional information (AI request). MDUFA Decisions for 510(k) submissions include findings of substantially equivalent or not substantially equivalent.

Resources:
FDA: 510(k) Submission Process
FDA: Recommendations for Dual 510(k) and CLIA Waiver by Application Studies
FDA: CLIA Waiver by Application
NIH SEED: 510(k) Pre-Submission Meetings
NIH SEED: 510(k) Documentation and Application

6 Prospective Human Testing

Unlike drug development, which generally involves a regimented three phase clinical trial process, IVDs may or may not require clinical trials; however, some form of testing human samples will likely be needed to show clinical and analytical validity. Generally, a human study is required when

one or more risks associated with the IVD cannot be fully mitigated through bench top testing or animal validation. When testing of human samples is needed, whether in a prospective clinical trial or other type of study/testing, it is important to coordinate with a local IRB to evaluate the safety and ethics of the human testing. In addition, the risk of the device study dictates the requirements for **IDE** review and approval under CFR Title 21 Part 812, as well as other regulatory requirements that must be met before beginning the IVD study.

NIH Institutes and Centers (ICs) have different levels (from none to full) of regulatory support for clinical investigations. Talk with the Program Officer for your award to ensure you know what resources may be available to you through NIH.

Please refer to the Regulatory Knowledge Guide for Therapeutic Devices for a more complete discussion of conducting human and clinical studies, including:

- Feasibility studies
- IDEs
- Risk determinations
- IRBs
- Usability testing

Please refer to the Regulatory Knowledge Guide for Digital Health for a more complete discussion of cybersecurity considerations and software documentation, including:

- Cybersecurity risk mitigation plans
- Documentation of software quality systems

6.1 IDE Regulation Exemption

Many IVD studies can be exempt from most provisions of the IDE regulation. An IVD device study is exempt from many requirements of 21 CFR Part 812 if the device meets an exemption under 21 CFR 812.2(c).

An IVD study is IDE exempt if it meets all the following conditions:

- **Is non-invasive**
- **Does not require an invasive sampling procedure that presents significant risk**
- **Does not introduce energy into a subject**
- **Is not used as a diagnostic procedure without confirmation of the diagnosis by another, medically established diagnostic product or procedure**
- **Is properly labeled for research or investigational use (RUO or IUO) in accordance with 21 CFR 809.10(c)**

A non-invasive device is one that does not, by design or intention, penetrate or pierce the skin or mucous membranes of the body, the ocular cavity, or the urethra; or enter the ear beyond the external auditory canal, the nose beyond the nares, the mouth beyond the pharynx, the anal canal beyond the rectum, or the vagina beyond the cervical os. Blood sampling that involves simple venipuncture is considered non-invasive, and the use of surplus samples of body fluids or tissues that are left over from samples taken for non-investigational purposes is also considered non-invasive.

FDA considers sampling techniques that require biopsy of a major organ, use of general anesthesia, or placement of a blood access line into an artery or large vein (subclavian, femoral, or iliac) to present a significant risk.

6.2 User-Driven Software Design Elements

Whether the end user of the IVD is a clinician, a patient at a clinic, or a family at home, it is important for the design of the device to meet user needs. When FDA reviews the software design as part of a Market Authorization application, it is checking to ensure that the work performed by the software developers is clear, is unambiguous, and has minimal ad hoc design decisions. There should be a reason for each design choice, and user needs should be met by the product as a whole.

For more information on usability testing, please refer to Section 2.6 of the Regulatory Knowledge Guide for Therapeutic Devices.

Resource:
NIH SEED: SaMD & AI/ML Workshop

7 Companion Diagnostics (CDx)

A CDx is a medical device, often an IVD, that provides information essential for the safe and effective use of a therapeutic product, such as a drug or biological product.

FDA published the "*In Vitro* Companion Diagnostic Devices" and "Developing and Labeling *In Vitro* Companion Diagnostic Devices for a Specific Group of Oncology Therapeutic Products." FDA also published a draft guidance document on the "Principles for Codevelopment of an *In Vitro* Companion Diagnostic Device with a Therapeutic Product." Most CDx are approved by FDA via the **PMA** regulatory pathway (with some exceptions).

The first approved CDx occurred with the approval of both the therapeutic product, Herceptin (trastuzumab) and the IVD, HercepTest™. The CDx (HercepTest) measures HER-2 (human epidermal growth factor receptor 2) expression levels in breast cancer tissue and identifies patients more likely to have a therapeutic response.

Some basic characteristics of CDx include:

- Can detect and measure biomarkers
- Is essential for the safe and effective use of a therapeutic product (use of a diagnostic is required in the labeling of the therapeutic product)
- Reference is made to the therapeutic product and information in the label of the diagnostic

FDA strongly encourages sponsors considering developing CDx devices to request a meeting with the relevant device review divisions (CDRH or CBER) as early in development as possible.

See the Regulatory Knowledge Guide for Small Molecules for more information on codeveloping an IVD with a therapeutic product.

Resources:
NIH SEED: Diagnostic Reimbursement Case Study 3 CDx

7.1 CDx Characteristics

In the context of CDx development, you may use a **biomarker** that enables better decision making on the use of a particular therapy tailored toward a subset of patients and disease categories.

Per FDA guidance, when use of a diagnostic device is required in the labeling of a therapeutic product, use of the diagnostic device is considered "essential" to the use of the therapeutic product. For example, an IVD may be a CDx if it is required for:

- Selection of appropriate patients for therapy
- Identifying patients who should not use the product
- Monitoring patients being treated with a certain product to achieve safety or effectiveness

7.2 Developing and Validating a CDx

If you are developing a test for a specific therapeutic product, the IVD should be developed at the same time as the therapeutic product to ensure concurrent approval/clearance of both products.

FDA reviews each CDx submission within the context of, or in conjunction with, its corresponding therapeutic product. The reviews of both the CDx and therapeutic product are carried out collaboratively among relevant FDA offices.

Before using a biomarker as part of a clinical trial for a drug, ideally you will have some data to support the use of the biomarker (e.g., cell-based or ***in vivo*** data). If you are developing the supporting data for the biomarker in partnership with the IVD innovator, it is important to have set testing processes and protocols that will be able to produce informative data. If a biomarker is being targeted for clinical use, it is important that the test used is clinically validated, which may be completed during clinical trials for

the drug. Specific clinical trial design considerations may be needed depending on how a biomarker test or tests are used for a clinical trial. The design of the clinical trial will be critical to providing sufficient and actionable data to support marketing clearance. Consultants experienced in clinical trial design and biostatistics can be helpful in developing a robust design.

Resource:
FDA: In Vitro Companion Diagnostic Devices

7.3 Repurposing an Existing IVD/CDx

While not an official term, industry describes a "follow-on" CDx as a device that (while not used in the original clinical trial) is developed after an already approved CDx has entered the market.

You may want to grow your market share by expanding the current label to other existing or new therapeutic products and/or indications for biomarkers covered by your assay. This is often the case for CDx developed for oncology therapeutic products.

Resource:
FDA: List of Cleared or Approved Companion Diagnostic Devices (In Vitro and Imaging Tools)

7.4 Regulatory Pathways for CDx

You are encouraged to request meetings with FDA's device and therapeutic review divisions early to ensure your product development plan will produce sufficient data to establish the safety and effectiveness of both products.

The regulatory pathway for a CDx, like for other devices, depends on the level of risk to patients. This includes the intended use of the CDx and the controls to ensure the safety and effectiveness of the device. The PMA and PMA supplements are usually the most utilized pathway for CDx. Consult with FDA early to determine which of the following regulatory pathways is most appropriate.

- **PMA:** CDx are high-risk devices and are classified as Class III devices. As a result, a PMA is required for most (Class III) CDx devices.
- **510(k):** A premarket notification submission or 510(k) may be an option for a CDx innovator if the CDx being developed is similar to an existing CDx on the market. A 510(k) may be appropriate for a broader labeling claim. FDA will assess whether a 510(k) or PMA is required for the device based on the intended use, technology type, and other factors—such as whether the existing technology can be used as a predicate device.
- **HDE:** Devices that are developed to address diseases and conditions that affect 8,000 or fewer patients per year nationwide may obtain **HUD** status from the FDA.

You should be cautious not to confuse CDx with a combination product, which is a product that is a combination of a drug, device, and/or biological product, and to ensure you know which regulatory

designation your product has. Please see the Combination Product Regulatory Guide for more information.

Resources:
NIH SEED: CDRH Small Business Support – The Division of Industry and Consumer Education (DICE)
NIH SEED: 510(k) Pre-Submission Meetings
NIH SEED: 510(k) Documentation and Application
NIH SEED: Navigating FDA: Device (and Diagnostic) Development Requirements

7.5 Other Considerations

LDTs: IVDs (including LDTs) are not permitted to use therapeutic product information as part of the test descriptions and/or intended use statements without seeking FDA approval. This is also the case for an LDT developed based on an existing CDx. Only IVDs that have FDA approval as a CDx are permitted to use therapeutic product information on the label or test descriptions.

LDTs and Single-Site PMAs: An LDT used in clinical trials with the therapeutic product can be brought to FDA as an IVD CDx for approval via a single-site PMA submission. As such, the diagnostic will have to be clinically validated. Clinical validation is required for all IVDs and is in addition to the analytical validation that is required for LDTs under the CLIA.

Pharmacogenomic (PGx) Test: PGx tests provide information regarding the role genetics may play in an individual's reaction to drugs. FDA states that "an *in vitro* PGx test would be considered a companion diagnostic device if it will provide information that is essential for the safe and effective use of a therapeutic product as directed in labeling."

Complementary Diagnostic: FDA determines whether a test is considered essential for the safe and effective use of the drug (i.e., a companion diagnostic). This determination is based on the clinical trial data presented to FDA by the therapeutic product and IVD innovator. There have been instances in which FDA determined that a test is not essential for the safe and effective use of the drug but is still useful in identifying a biomarker-defined subset of patients that responds differently to a drug and aids in the risk/benefit assessment for individual patients. These may be called CDx (although FDA has not formally defined that term) and the tests may be referred to in the product labeling, such as in the clinical trials, or other sections.

Combination Products: In addition, you may be developing a **combination product**—a product that is a combination of a drug, device, and/or biological product. For instance, some fluorescence *in situ* hybridization (FISH) tests listed on FDA's website are considered combination products. While most therapeutic products and IVD CDx device pairs will not meet the definition of combination product, it is beneficial to be familiar with the definition. Per the 2014 FDA guidance document:

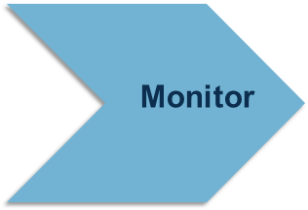
- It is not necessary to contact the Office of Combination Products about whether a therapeutic product and IVD CDx device pair is a combination product unless recommended by CDER, CBER, or CDRH.

- FDA intends to require separate marketing applications for a therapeutic product and an IVD CDx device intended for use with that therapeutic product regardless of whether the products could constitute a combination product.

Clinical Trial Assays (CTA): CTAs are IVDs that are currently under development and not approved for clinical diagnostic use. These assays are used in clinical trials to select subjects or investigate a hypothesis related to outcome. CTAs may be used to design IVDs that are intended to be marketed as a CDx in the future. In most circumstances, such IVDs and CTAs will need to follow IDE regulations. This is the case, as the device could pose significant risk to trial participants if used to make critical treatment decisions, such as patient selection, treatment, or treatment arm assignment.

Disease- or Condition-Specific Diagnostic Products: If you are developing a CDx for defined subgroups of patients for a disease-specific drug or biologic, any applicable FDA guidance documents should be consulted as part of the product development phase.

Resources:
FDA: Developing and Labeling In Vitro Companion Diagnostic Devices for a Specific Group of Oncology Therapeutic Products
FDA: Clinical Pharmacogenomics: Premarket Evaluation in Early-Phase Clinical Studies and Recommendations for Labeling
FDA: Table of Pharmacogenetic Associations
FDA: List of Cleared or Approved Companion Diagnostic Devices (In Vitro and Imaging Tools)



8 Quality Management Systems (QMS)

The primary regulatory concern with respect to manufacturing is the presence of a QMS. After a device is on the market, the manufacturer may be inspected by FDA at any time, and the manufacturing processes will be a large focus of that inspection. The analytical validity (Section 3) and the clinical validity (Section 4) of the IVD should be not only documented in the Market Authorization application to FDA, but also recorded and maintained within the QMS. Medical devices, including IVDs, must follow additional FDA requirements once they are cleared or approved for market. These requirements extend beyond the QMS and include the sharing of safety-related data to FDA when adverse events occur.

Please refer to Section 6 of the of the Regulatory Knowledge Guide for Therapeutic Devices for more information regarding QMS of medical devices, including:

- International Organization for Standards
- Current Good Manufacturing Process
- QMS Implementation

Resource:
NIH SEED: Quality Management System for Medical Devices

9 Modifying a Device After Market Authorization

If an IVD device has been previously cleared or approved by FDA, changes may require a new submission.

For a more detailed discussion about making changes to existing devices, including IVDs, please refer to Section 7 of the Regulatory Knowledge Guide for Therapeutic Devices.

9.1 Minor Changes to an IVD

If you are making a change to the form or function of a device that does not change the intended use or risk level of the technology, you may have an opportunity for a more straightforward regulatory path. For very minor changes, such as bug fixes related to a diagnostic's software interface—i.e., changes that do not impact the functionality, claims, risk, underlying technology—a new submission to FDA may not be necessary at all, but the changes must be documented in the QMS.

9.2 New Clinical Trials

When an already marketed diagnostic testing research project begins a new clinical trial, it is important to determine whether the trial is studying the drug or biologic, the diagnostic test itself, or a combination CDx. When major changes or supplements to an existing IVD are proposed, a new clinical trial may need to be designed. When testing of human samples is needed, whether in a clinical trial or other type of study/testing, it is important to coordinate with a local IRB to evaluate the safety and ethics of the human testing.

9.3 Real-World Evidence from Routine Clinical Care

Some IVDs on the market involve extensive collection of data as part of routine clinical care. Currently marketed devices with a large pool of existing clinical data—also called **real-world data**—may use that data as evidence to support a new design or intended use for the device. FDA calls this type of supporting information **real-world evidence** (RWE). While RWE has been used in regulatory decision-making by CDRH for medical devices, there is less experience using RWE for IVDs. To date, only a few innovators have used RWE in their submissions. However, RWE may play an increasing role in future clinical trials and post-market reviews and you should request a pre-submission meeting with CDRH to explore if this approach is right for your IVD.

9.4 New Intended Use

If you are developing a currently marketed device, you might be exploring a new use case for the technology. This can happen even if the underlying technology is completely unchanged. For example, an existing IVD may be used for the detection of human immunodeficiency virus (HIV), but you may be

testing it for detection of SARS-CoV-2 (the virus that causes COVID-19.) If a new intended use is proposed, then it is likely that an entirely new FDA submission will be needed.

If you are proposing a new intended use, you will need to request a new Market Authorization from FDA.

9.5 Benefit-Risk Ratio

Changes to an IVD, or its intended use, could create new risk and may impact the risk classification for a device. This change in risk classification may affect the regulatory pathway. For example, a human chorionic gonadotropin test system for the early detection of pregnancy can be a Class II (moderate to high risk) device. But if the test system is intended to be used for anything other than early detection of pregnancy, such as for the diagnosis of germ cell tumors, then it becomes a Class III (high risk) device, due to increased complexity and more potential for adverse events from inaccurate results. In most cases, the expectation is that new benefits will outweigh new risks.

Resources:
FDA: Factors to Consider When Making Benefit-Risk Determinations in Medical Device Premarket Approval and De Novo Classifications
FDA: Risk and Risk Mitigation Case Study

9.6 Evidence from Outside the U.S.

Evidence of device performance collected elsewhere in the world can help support an FDA premarket application—for example, test results based on international standards. However, if performance data is gathered exclusively outside the U.S., it may not be sufficient to support an FDA Market Authorization request.

Please refer to Section 7.1 of the Regulatory Knowledge Guide for Therapeutic Devices for more information.

10 Market Expansion Activities

For IVDs that are already on the market, you may have plans to expand your footprint and market size in the U.S. through strategic partnerships with distributors, **direct-to-consumer** (DTC) marketing, or other business development activities. Note that international market expansion practices are not covered in this guide

10.1 CLIA Complexity Categorization

CLIA categorization is determined after FDA has cleared or approved a marketing submission, or upon request for legally marketed devices. Tests are stratified into one of the following categories:

- **Waived**
- **Moderate complexity**
- **High complexity**

Tests that are either waived by regulation under 42 CFR 493.15(c) or are approved for home-use or OTC use are automatically categorized as waived. Otherwise, based on review of the package insert instructions, a test is graded for level of complexity by assigning scores of 1, 2, or 3 for each of the seven criteria, when added together, determine whether the test is moderate or high complexity. Tests with a score above 12 are categorized as high complexity; tests with a score below or equal to 12 are categorized as medium complexity. FDA usually communicates their decision on the complexity categorization within two weeks of a positive marketing decision.

The 7 categorization criteria are:

- Knowledge
- Training and Experience
- Reagents and Materials Preparation
- Characteristics of Operational Steps
- Calibration, Quality Control, and Proficiency Testing Materials
- Test System Troubleshooting and Equipment Maintenance
- Interpretation and Judgment

Categorization Criteria	Score of 1: Indicates the lowest level of complexity	Score of 3: Indicates the highest level of complexity	Final Score (1, 2, or 3)*
1. Knowledge	(A) Minimal scientific and technical knowledge is required to perform the test; and (B) Knowledge required to perform the test may be obtained through on-the-job instruction.	Specialized scientific and technical knowledge is essential to perform preanalytic, analytic, or postanalytic phases of the testing.	
2. Training and Experience	(A) Minimal training is required for preanalytic, analytic and postanalytic phases of the testing process; and (B) Limited experience is required to perform the test.	(A) Specialized training is essential to perform the preanalytic, analytic, or postanalytic testing process; or substantial experience may be necessary for analytic test performance.	
3. Reagents and Materials Preparation	(A) Reagents and materials are generally stable and reliable; and (B) Reagents and materials are prepackaged, or premeasured, or require no special handling, precautions or storage conditions.	(A) Reagents and materials may be labile and may require special handling to assure reliability; or (B) Reagents and materials preparation may include manual steps such as	

Categorization Criteria	Score of 1: Indicates the lowest level of complexity	Score of 3: Indicates the highest level of complexity	Final Score (1, 2, or 3)*
		gravimetric or volumetric measurements.	
4. Characteristics of Operational Steps	Operational steps are either automatically executed (such as pipetting, temperature monitoring, or timing of steps), or are easily controlled.	Operational steps in the testing process require close monitoring or control, and may require special specimen preparation, precise temperature control or timing of procedural steps, accurate pipetting, or extensive calculations.	
5. Calibration, Quality Control, and Proficiency Testing Materials	(A) Calibration materials are stable and readily available; (B) Quality control materials are stable and readily available; and (C) External proficiency testing materials, when available, are stable.	(A) Calibration materials, if available, may be labile; (B) Quality control materials may be labile, or not available; or (C) External proficiency testing materials, if available, may be labile.	
6. Test System Troubleshooting and Equipment Maintenance	(A) Test system troubleshooting is automatic or self-correcting, or clearly described or requires minimal judgment; and (B) Equipment maintenance is provided by the manufacturer, is seldom needed, or can easily be performed.	(A) Troubleshooting is not automatic and requires decision-making and direct intervention to resolve most problems; or (B) Maintenance requires special knowledge, skills, and abilities.	
7. Interpretation and Judgment	(A) Minimal interpretation and judgment are required to perform preanalytic, analytic and postanalytic processes; and (B) Resolution of problems requires limited independent interpretation and judgment.	(A) Extensive independent interpretation and judgment are required to perform the preanalytic, analytic or postanalytic processes; and (B) Resolution of problems requires extensive interpretation and judgment.	
		TOTAL SCORE	

Table 1. CLIA Categorization Criteria and Scoring

*Note: Per FDA, a score of 2 will be assigned to a criterion when the characteristics for a particular test are intermediate between the descriptions listed for scores of 1 and 3.

During a public health emergency, FDA may issue EUAs for IVDs. FDA does not issue CLIA complexity categorizations for tests under an EUA; rather FDA deems a test appropriate for a certain category and issues the EUA for a certain setting, e.g., for point-of-care (POC) testing.

Resource:
FDA: CLIA Categorizations
FDA: Administrative Procedures for CLIA Categorization

10.2 CLIA Waiver Status for POC Testing

Often, the terms "POC" testing and "CLIA waived" testing are used interchangeably, but important and subtle differences exist that impact how such tests are regulated and marketed. The Centers for Disease Control and Prevention defines POC testing as: "a phrase used to describe the location where testing is performed, such as at the bedside or near the site of patient care." While some POC tests are approved for a CLIA waiver, advances in technology that enhance the rapidity of testing enable more complex, nonwaived testing to be performed at or near the site of patient care. If the innovator asks to receive POC authorization from FDA, they are generally referring to receiving CLIA waiver status from FDA, so that the test may be performed at sites that have a **CLIA Certificate of Waiver** to perform low complexity tests.

If you intend to offer an IVD at the POC, FDA must first categorize the test as a CLIA waived IVD following clearance or approval. This designation indicates that the test is both simple to use and offers a low risk of inaccurate results. The relationships between FDA application types, test complexities, and corresponding CLIA certifications are illustrated in Figure 4.

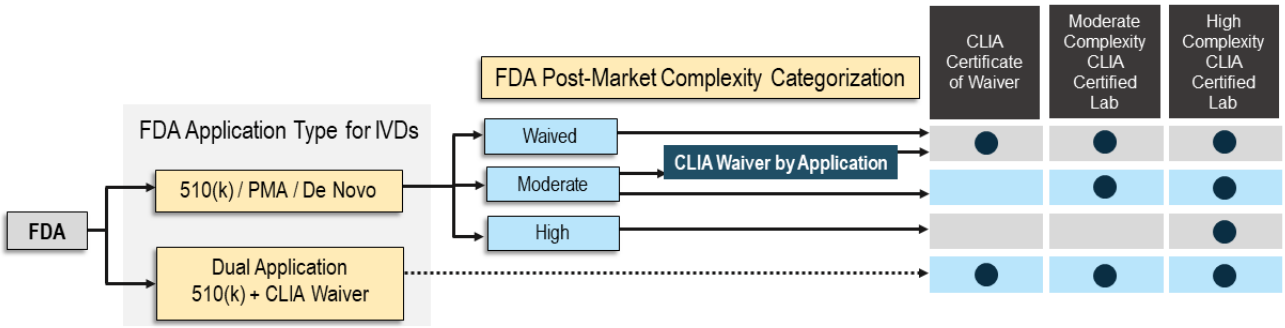


Figure 4. FDA CLIA complexity categorizations by FDA application type

The FDA automatically categorizes IVDs that are cleared or approved for home-use or OTC use as waived. If the IVD is a moderate complexity device (as classified by the FDA post market approval), consider applying for CLIA waived status through a CLIA Waiver by Application submission to FDA. High complexity IVDs cannot be changed to a CLIA waived category.

Resources:
FDA: Recommendations for Clinical Laboratory Improvement Amendments of 1988 (CLIA) Waiver Applications for Manufacturers of In Vitro Diagnostic Devices
Webinar: Clinical Laboratory Improvement Amendments of 1998 (CLIA) Waiver Applications Final Guidance

10.3 OTC Offerings

When a device is offered OTC, the device must be simple enough to be used by a layperson and can be purchased without a prescription. A sample collection kit, a diagnostic device, or "all-in-one" devices can be offered OTC. All-in-one tests can be completed at home by a consumer from start to finish—from sample collection to performing the test and result interpretation; no part of the process involves a lab.

If only a sample collection kit can be purchased OTC (without a prescription), then the sample must still be sent to a lab to be performed, analyzed, and reported. These devices require FDA's clearance or approval for DTC marketing. To receive FDA's approval to offer a device without a prescription (e.g., in an online drug store), there must be sufficient clinical and usability data to show that the test can be performed by a layperson. A home-use pregnancy test is an example of an OTC device. An example of a company that received OTC classification for its molecular Cancer Predisposition Risk Assessment System is 23andMe.

Resource:
FDA: FDA OTC Database

10.4 Prescription Home-Use Offerings

Another way to expand market potential for a device is through home-use (also called "at-home" use). Home-use offerings describe sample collection devices a patient receives, usually in the mail, to collect a specimen (e.g., saliva or urine) at home for a test prescribed by a healthcare provider. From a regulatory perspective, there are two components to home-use testing: the sample collection kit and the diagnostic device (sample testing.) If they are not part of an "all-in-one" device, FDA reviews these components as two separate IVDs.

A prescription home-use IVD can be both a collection device and an assay device. While most prescription home-use IVD developers utilize only the collection device for home-use and have the patient send the sample to a laboratory for processing, some IVD developers may opt to use an IVD intended for OTC use (without a prescription) as a prescription home-use device first. This allows the IVD to enter the market more quickly and collect additional data later for the human usability studies needed for an OTC claim. An example of a prescription home-use test with a collection plus assay component are saliva collection devices for COVID-19 testing. An example of a prescription home-use collection device IVD is certain carrier screening tests, such as for cystic fibrosis.

10.5 Direct to Consumer (DTC) Offerings

FDA defines DTC tests as devices that are marketed directly to individuals without the involvement or guidance of a healthcare provider. FDA has determined that this category of IVDs carries additional risk, since they are being performed by a consumer rather than by a healthcare professional. Often, these tests include home-use sample collection devices.

Updated October 2023