A PROPOSED REGULATORY FRAMEWORK FOR *IN VITRO* CLINICAL TESTS

Diagnostic Test Working Group

August 14, 2015

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This document sets forth a revised consensus proposal for a new regulatory scheme for *in vitro* clinical tests prepared by the Diagnostic Test Working Group (DTWG), a coalition of leading diagnostic manufacturers and clinical laboratories. This updated white paper addresses a number of suggestions and comments received by DTWG members in response to the March 2015 white paper. Each Coalition member must obtain final senior executive approval of the final, complete proposal.

1. Background

In vitro clinical tests are tests that can detect analytes, diseases, genetic anomalies, conditions or infections, predict health outcomes, or help guide therapy. Some tests are used in laboratory or other healthcare professional settings, and other tests are used by consumers outside of a healthcare facility at home. A laboratory developed test (LDT) is a type of test designed, developed, and performed within a single laboratory entity. LDTs have sometimes been referred to as "in-house developed" tests.

Currently, the Federal Food, Drug and Cosmetics Act (FD&C Act) grants the U.S. Food and Drug Administration (FDA) the authority to regulate the sale and distribution of medical devices. FDA asserts that it also has the legal authority to regulate LDTs as medical devices under the FD&C Act. Since 1976, FDA has chosen in many circumstances to exercise its enforcement discretion to not regulate LDTs; however, it has recently announced its intention to begin regulating LDTs as medical devices.[1] FDA recently issued draft guidance documents on its proposed regulation of LDTs. The guidance documents set forth the FDA's plan to regulate LDTs using existing medical device regulatory systems.

CMS has authority to regulate laboratory operations and therefore LDTs through the Clinical Laboratory Improvement Amendments of 1988 (CLIA). CMS regulates the quality of clinical laboratories and the clinical testing process. CLIA regulations seek to ensure reliable test results through focusing on the quality of the laboratory procedures and personnel. CLIA also seeks to ensure that the LDT accurately detects the presence or absence of the target analyte(s) in a patient specimen (also known as analytical validity).

Determining the appropriate regulatory oversight system for *in vitro* diagnostic tests is important to patients, health care providers, manufacturers and laboratory companies.

Finally, the practice of medicine involved in consultations about, and the interpretation of, the test results is a wholly separate concept that must remain outside of the regulatory construct of either the development or conduct of the test. This proposal discusses how these lines should be drawn and the key criteria separating each of these activities. To the extent there is currently overlap between the requirements of the FD&C Act and CLIA, this proposal seeks to reduce

[1] FDA's regulatory authority over LDTs has been the source of significant disagreement. Certain stakeholders dispute FDA's jurisdiction over LDTs while other stakeholders have criticized FDA for not regulating LDTs.

duplication and improve efficiencies by having one entity regulate activities within its respective authority.

2. Policy Objectives

With the recent technologic and scientific developments in genetic tests and other clinical tests, there are great opportunities to improve public health and advance the future of personalized medicine. However, inappropriate governmental oversight can present challenges to the development and use of new and innovative technologies. It is necessary to create the appropriate regulatory construct to promote the development of new, innovative clinical test technology and continued patient access while balancing the need to ensure that clinical tests are accurate and reliable.

This proposal seeks to advance several core policy objectives:

1. Provide high-value, analytically and clinically valid clinical tests for patient benefit in a timely manner.
2. Provide uniform, efficient access to diagnostic testing to all who require it.
3. Advance value-added innovation.
4. Promote timely and predictable regulatory processes.
5. Regulate clinical tests based on the intended use and risks of such tests.
6. Match regulation to risk.
7. Avoid non-value-added and duplicative regulation.
8. Regulate the same activity the same way (*i.e.*, similar tests or activities are governed by the same regulatory principles).
9. Promote transparency, certainty, clarity, and simplicity (without foreclosing appropriate flexibility).
10. Maintain the practice of medicine.
11. Recognize the importance of the ability to share scientific information.

3. Key Concepts

3.1. IVCTs are Fundamentally Different

In vitro clinical tests are fundamentally different than medical devices. Traditional medical devices either provide therapy (*e.g.,* a knee implant or pacemaker) or are tools used to provide therapy (*e.g.*, a scalpel or infusion pump). Typically, traditional medical devices actually touch the patient and have a direct impact on patient outcomes. Such traditional products must provide a reasonable assurance of safety and efficacy.

In contrast, *in vitro* clinical tests are used to provide information, often for use by a health care professional,[2] in making treatment or health-based decisions. While "safety and effectiveness" is

[2] Consumer diagnostic products either provide data of such common knowledge that a health care professional is not needed to assist in the interpretation of the test results or a health care professional has already provided (in one form or another) an interpretive schema for the test results.

a critically important objective for therapeutic products, these concepts are not the key attributes of a diagnostic test. The key attributes of a diagnostic test are that it provides analytically valid and clinically valid information which is then used, often by health care professionals, to make decisions related to patient care.

The innovation process for therapeutic devices differs greatly from the innovation process for *in vitro* clinical tests. There are different needs for physician input, features, and risk assessments. Likewise, the design and testing of a diagnostic test is usually quite different from what is required for a therapeutic product or device. Other than sample derivation, an *in vitro* clinical test rarely touches a patient and therefore does not present the questions of "safety" that exist with medical devices.

In summary, as compared to traditional therapeutic medical devices, *in vitro* clinical tests fulfill different purposes, are developed differently, and have different critical outputs. Therefore, the same regulatory system does not rationally meet the needs of both therapeutic medical devices and *in vitro* clinical tests.

This proposed regulatory structure recognizes these differences and sets forth a regulatory system that is tailored to *in vitro* clinical tests and advances the above policy goals, specifically patient benefit, and innovation.

3.2. Covered Tests

This proposal applies to all *in vitro* clinical tests (IVCTs).

> An ***in vitro clinical test*** is any finished product or laboratory test protocol intended by the developer to be used in the collection, preparation, analysis,[3] or in vitro clinical examination of specimens taken or derived from the human body, solely or principally for the purpose of identifying, measuring, predicting, monitoring, or assisting in selecting treatment for, a disease or other condition; provided however, provided however, that laboratory tests that meet the definition of a "biologic" under Section 351 of the Public Health Service Act, and which are either intended to screen human blood, human cells, tissues, or cellular or tissue-based products (HCT/Ps), and organs for infectious diseases or intended to determine donor/patient compatibility to ensure safe transfusion or transplantation of blood, human cells, tissues, or cellular or tissue-based products (HCT/Ps), and organs, are not in vitro clinical tests but rather will be regulated under Section 351 of the Public Health Service Act.

[3] This is intended to capture software, to the extent otherwise regulated.

IVCTs are not drugs or devices as defined in section 201 of the Federal Food, Drug, and Cosmetic Act or biological products subject to section 351 of the Public Health Service Act (except as stated above).

A ***laboratory test protocol*** is the final design of a test not produced as a finished product or purchased as a finished product from a third party.[4] This protocol does not include development of standard operating procedures for performance of an IVCT.

A ***finished product*** is an article of personal property other than a laboratory test protocol that is suitable for use and capable of functioning for its intended purpose without further production activity.[5] A component or raw material is not a finished product, nor a drug, device, or biological product.[6]

The following are outside the scope of the definition of IVCT:

- Forensic tests.
- Drug-of-abuse testing for non-clinical purposes.
- Genetic tests for non-clinical purposes.

A key difference between the proposed definition and the current FD&C Act definition of "*in vitro* diagnostic test" is that IVCTs will be treated as a standalone regulatory category—IVCTs are not medical devices, drugs, or biologics.[7]

The definition of an IVCT includes platforms used to "run" tests, but some regulatory requirements for platforms vary.

A platform is an article comprised of hardware and, in many cases, software that is designed and intended by the developer to perform multiple different* in vitro *clinical tests.

Platforms are discussed in greater detail in section 7.1.

3.3. Activity-Based Approach

A regulatory framework for IVCTs should be focused and based on the various types of *activities* involved in creating and conducting an IVCT. The existing regulatory structure, under which regulatory requirements are tied to the type of entity (*i.e.*, a manufacturer or a laboratory),

[4] This is distinct from the laboratory's standard operating procedure (SOP), which describes the process or service of actually performing the test.
[5] This does not include analyte specific reagents (ASRs). ASRs will be treated as raw materials, and thus can be combined by a developer, which is a public health benefit. The definition of finished product does include standalone software.
[6] Supplier controls adequately protect patients. This structure is similar to the current regulatory approach for HCT/P blood products.
[7] The new definition increases regulatory focus and efficiency by concentrating on finished products and laboratory test protocols rather than raw materials or components.

results in disparate regulation. Furthermore, the amorphous distinction between types of entities engaged in identical or similar activities results in confusion, inconsistent regulation, regulatory gaps, and overlapping requirements. Therefore, it is critical that each activity involved in creating and conducting an IVCT be subject to certain regulatory requirements regardless of the type of entity engaging in the activity. This activity-based approach is fundamental to the proposed framework.

This proposed framework is based on the ten activities in the life cycle of an IVCT, shown in Figure 1, below.

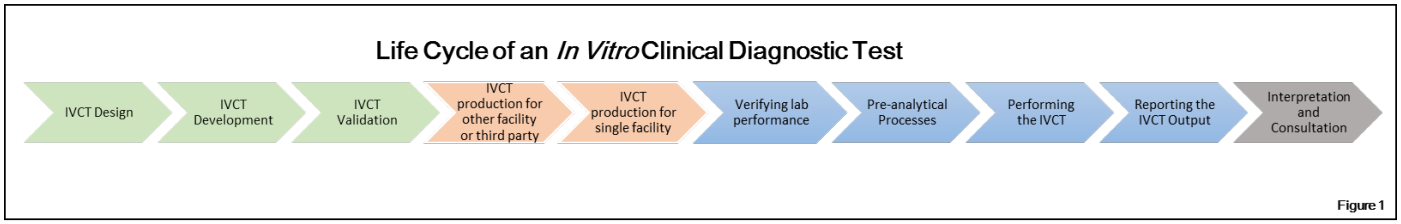


Figure 1

The 10 steps in the IVCT life cycle are:[8]

1. **IVCT Design.** The process begins by establishing the relevant and applicable physical, performance, packaging, and labeling requirements of an IVCT. This process takes into account multiple stakeholder requirements, including patient and physician, laboratory use, and regulatory requirements.
2. **IVCT Development.** The next step in the process is taking the IVCT from initial design to either a laboratory test protocol or a set of final procedures and specifications to enable production of a finished product.
3. **IVCT Validation.** This is the set of processes that are used to confirm that the design and development outputs meet the design inputs and the intended use requirements for the applicable environment.
4. **IVCT Production for Another Facility or Third Party.** These activities include production, packaging, and labeling an IVCT for distribution to another facility or third party.
5. **IVCT Production for a Single Facility.** Reagents and materials are prepared by a laboratory according to the specifications of the IVCT protocol for performance of an IVCT on patient specimens. This activity is limited to the preparation of reagents and materials to be used by the CLIA laboratory that performs the IVCT protocol on patient specimens.
6. **Verifying Laboratory Performance.** Verification of performance is the process of ensuring that the IVCT, when performed in the laboratory by the laboratory's testing personnel and with the facility's patient population, is performing as the IVCT developer intended.

[8] These descriptions of the steps in the IVCT life cycle are not comprehensive or definitional; rather, they are simply intended to illustrate the typical process of developing and performing an IVCT.

7. **Pre-Analytical Processes.** A number of steps are required before the IVCT can be "run." These include processes for proper test ordering, patient specimen collection, specimen labeling, specimen transportation, and specimen processing to prepare the patient specimen for testing.
8. **Performing the IVCT.** This is often referred to as the analytical testing process. It is the process of actually "running" the *in vitro* clinical test in accordance with the standard operating procedures.
9. **Reporting the IVCT Output.** This is often referred to as the post-analytical process. The IVCT will produce an output of information. The output can take a variety of formats depending upon the specific test, including raw data, a binary result, a diagnosis, or treatment information.
10. **Interpretation and Consultation.** Commonly the IVCT output must be interpreted by a health care professional to be used for meaningful diagnostic or medical purposes. In some instances, the output will not provide meaningful medical information unless interpreted by a specialist. In other instances the output will be easily understood by the relevant health care professional, but the health care professional will use the information for purposes of a professional consultation with the patient.

For purposes of this proposal, the ***developer*** is any entity engaged in:

- The design, development, or validation of the IVCT; or
- The production of a finished product.

The ***laboratory operator*** is any entity engaged in:

- The preparation of reagents or other test materials for use only in its facility;
- Verifying laboratory performance for the IVCT;
- Development of a standard operating procedure for performance of an IVCT;
- Pre-analytical processes for the IVCT;
- Performing patient-specific IVCTs; or
- Reporting the output of an IVCT.[9]

3.4. Risk-Based Approach

The proposed framework is also a risk-based regulatory framework. A regulatory framework for IVCTs must balance patient value, timely physician and patient access to new and innovative tests, and reasonable assurances of analytical and clinical validity. Therefore, only regulation that is necessary to provide a reasonable assurance of analytical validity and clinical validity should be imposed. The level of regulation must be matched to the risk-level of the relevant IVCT to ensure that patient access and innovation are not unduly hampered.

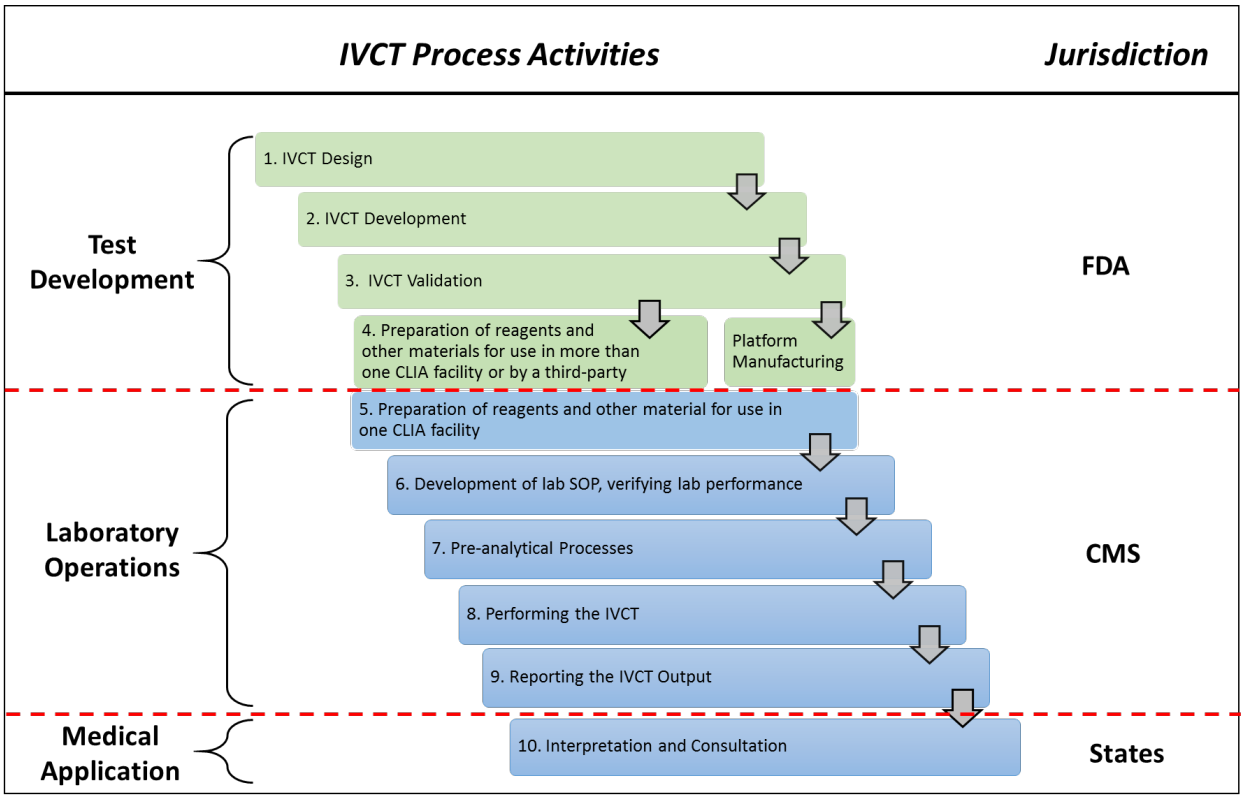
[9] Neither the term *developer* nor *laboratory operator* is intended to encompass the practice of medicine. As used here, "reporting the output of an IVCT" does not include the interpretation of an IVCT output by a pathologist, laboratory physician, or laboratory scientist (Ph.D.) or the reporting of such interpretation by such professional.

4. Jurisdiction

Consistent with the activity-based approach described above, the relevant regulatory authority with jurisdiction should be determined on an activity-by-activity basis. The delegation of jurisdiction should be based on the following realities:

- The process of developing an IVCT (*i.e.*, design, development, and validation) is uniquely different from the process of performing an IVCT (*i.e.*, actually testing a specimen) that has already been developed.
- Existing regulatory authorities have important existing competencies with regard to development of IVCTs and with regard to the operation of laboratories that run IVCTs.
- The practice of medicine must be preserved.
- Clear jurisdictional lines of demarcation are needed to promote certainty and efficiency.
- Any one activity should be regulated under only one system. Duplicate regulation, including regulation of the same activity by different government bodies, must be prevented.

Drawing upon those principles and the traditional regulatory competencies of the relevant agencies, jurisdiction will be divided among FDA, CMS, and the States. FDA will have jurisdiction over test development activities, including IVCT design, IVCT development, IVCT validation, the production of reagents or test kits for distribution, and certain post-market activities. CMS will retain jurisdiction over laboratory operations, which will include the preparation of reagents for a single laboratory facility and the process of actually performing an IVCT. The practice of medicine—primarily in the medical judgment used for determining what tests are appropriate for a specific patient and the interpretation of test results and related consultations—will be reserved to the States. This jurisdictional scheme is shown in Figure 2, below, and is described in more detail in the following subsections.



This activity-based approach facilitates application of the same regulatory requirements to the same activity while also drawing clear lines of exclusive jurisdiction between FDA, CMS, and the States. Because jurisdiction is tied to specific activities, not specific entity type, a single entity can come under the jurisdiction of more than one regulatory authority for different activities. A single entity can engage in test development activities under FDA jurisdiction for one IVCT and engage in laboratory operations under CMS jurisdiction for a different IVCT. Similarly, with regard to a single IVCT, a single entity can engage in both test development activities under FDA jurisdiction and laboratory operation under CMS jurisdiction.

4.1. FDA Jurisdiction Over IVCT Development

The FDA has traditionally had jurisdiction over the development of medical products, and it has significant institutional capacities with regard to the systems and processes that are typically leveraged to ensure the quality and validity of the development process. It is therefore logical to grant FDA exclusive jurisdiction over test development activities and certain life cycle activities for the test. For this purpose, test development activities include:

- Design of an IVCT.
- Development of an IVCT.
- Validation of IVCT test performance.
- The production of a finished product.

- Modifications to IVCTs that have a meaningful clinical impact or change the IVCT's intended use.

A new center will be established within FDA to exercise the authority granted to it with respect to IVCTs.[10]

4.2. Jurisdiction Over Reagent Preparation

Following the development of an IVCT, but prior to the process of actually performing the IVCT, reagents and other materials must be prepared.[11]

Consistent with FDA's historical regulatory authority over manufacturing processes, FDA will have exclusive jurisdiction over the preparation of reagents and other materials that will be used by a third party or a CLIA facility other than the facility that conducts the preparation *(e.g.*, a separate CLIA facility under common ownership). Similarly, FDA will have exclusive jurisdiction over the manufacture of platforms. These activities are considered part of test development, as that term is used in this proposal.

The preparation of reagents for use within a single facility is closely tied to laboratory operations.[12] The Center for Medicare and Medicaid Services—specifically the Division of Laboratory Services—has significant institutional knowledge with regard to these activities. Therefore, CMS will have exclusive jurisdiction over the preparation of reagents and other material for use within the single CLIA facility that conducts the preparation of those reagents and other materials. These activities are considered laboratory operations, as that term is used in this proposal.

For this purpose, a ***facility*** means a single establishment with a unique CLIA certificate.[13]

4.3. CMS Jurisdiction Over Lab Operations

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[10] There are many advantages to establishing a new center within FDA to regulate IVCTs, including:
- Establishing a new center would send a clear message of the need for an updated IVCT regulatory system.
- Over time, it will be easier to maintain or increase the separation between IVCTs and therapeutic products.
- A new center will enhance the focus on IVCTs.
- The new center would have dedicated policy personnel.
- The process for developing implementing regulations will be more streamlined.
- Oversight of a center's performance is easier than oversight of an office.
- A new center would help address the concerns some stakeholders have with any FDA oversight of laboratory developed tests.

[11] For example, samples need to be collected and prepared. A platform may need to be readied, materials for that specific test may need to be mixed or prepared, and material may need to be loaded into a piece of hardware.

[12] The process of preparing materials (reagents, instruments, etc.) to perform patient testing is part of the core set of CLIA obligations. Quality control requirements, calibration requirements, etc. are embedded in the CLIA standards. Laboratories prepare reagents according to specifications in a laboratory test protocol and/or according to package insert directions for a finished IVCT product. This process needs to remain under the control of the laboratory as long as the reagents are used in a single facility.

[13] Note, however, a laboratory protocol can be shared among multiple facilities within a corporate family. This is discussed in greater detail in Section 5.2.

CMS has extensive institutional knowledge and capacity with regard to laboratory operations.[14] CMS will therefore have jurisdiction over laboratory operations, which will be defined to include:

- Procurement, preparation, storage, and shipment of patient specimens.
- Development of laboratory facility standard operating procedure for performing the test.
- Modifications to the developer's protocols that do not have a meaningful clinical impact or change the IVCT's intended use.
- Verifying laboratory performance.
- Pre-analytical processes.
- Performing the test pursuant to the relevant standard operating procedure.
- Reporting the results of an IVCT.[15]

4.4. Preserving the Practice of Medicine

Any regulatory scheme for IVCTs must preserve the professional practice and judgment of physicians and other health care professionals. Physicians and other health care professionals engage in professional practice in numerous ways with regard to IVCTs. The practice of medicine and other professions has long been the province of the States. States should retain jurisdiction over the practice of medicine. Specifically, with regard to IVCTs, the following should be reserved for State jurisdiction as part of the practice of medicine or other professions when undertaken by a pathologist, laboratory physician, or laboratory scientist (Ph.D.):

- Recommending appropriate patient specific diagnostic tests.
- Rendering a diagnosis as a result of a specimen review.
- Interpretation of data generated by an IVCT that otherwise would not be easily interpretable by a less specialized health care professional.
- Dialogue with a health care professional regarding scientific information about an IVCT.
- Assessment of an IVCT output related to a specific patient.

5. Regulatory Requirements for IVCT Development

The regulatory scheme for IVCTs should be risk-based. Different IVCTs present very different risks, and regulatory requirements should vary with risk to balance patient access and innovation with the need to provide a reasonable assurance of analytical validity and clinical validity.

[14] CMS regulates all laboratory testing performed on humans in the U.S. through CLIA, with few exceptions (*e.g.*, research testing that does not include patient specific test reporting). In total, CLIA covers approximately 244,000 laboratory facilities. The Division of Laboratory Services, within the Survey and Certification Group, under the Center for Clinical Standards and Quality, has the responsibility for administering the CLIA Program. The objective of the CLIA program is to ensure accurate and reliable test results by all laboratories regardless of location or whether a laboratory bills Medicare or Medicaid.

[15] This does not include the interpretation of an IVCT output by a pathologist, laboratory physician, or laboratory scientist (Ph.D.) or the reporting of such interpretation by such professional.

5.1. Risk Classifications

All IVCTs will be classified as high-risk, moderate-risk, or low-risk tests. The premarket, quality, and post-market requirements will vary by risk class.

RISK CLASSIFICATIONS

High Risk: An IVCT for which the IVCT developer makes specific claims that the IVCT provides information that identifies, measures, predicts, monitors, or assists in selecting treatment for, a serious or life-threatening disease or disorder, and such information is intended to be the sole determinant for directing or changing clinical treatment; provided, however, that an IVCT that is well characterized or for which a wrong result is not likely to have a significant impact on patient outcome or public health is a moderate-risk IVCT.

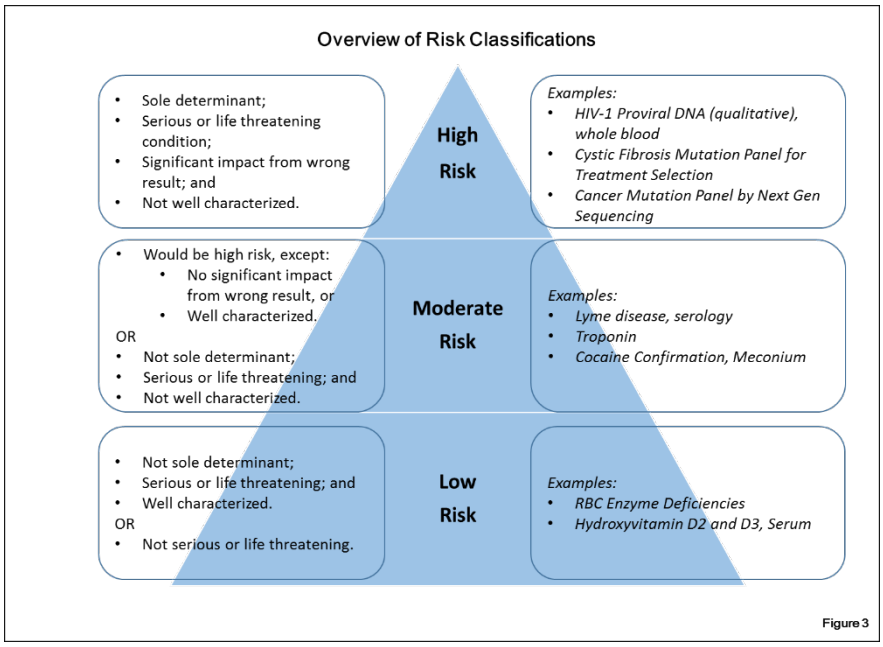
Moderate risk: An IVCT that would be high-risk except that it is well characterized, or for which a wrong result is not likely to have a significant impact on patient outcome or public health; or, an IVCT for which the IVCT developer makes specific claims that the IVCT provides information that identifies, measures, predicts, monitors, or assists in selecting treatment for, a serious or life-threatening disease or disorder, and such information is intended to be used only as adjunctive information to other health or diagnostic information in directing or changing clinical treatment; provided, however, that IVCTs that are not sole-determinants and are well characterized, are low-risk IVCTs.

Low Risk: An IVCT that is not a high-risk IVCT or moderate-risk IVCT.

A summary of the risk classifications is provided in Figure 3.

For purposes of risk classification, a ***serious or life-threatening disease or disorder*** is a disease or condition:

- for which the likelihood of death within one year is high unless the course of the disease is interrupted;
- which results in permanent impairment of a body function or permanent damage to a body structure within one year unless the course of the disease is interrupted; or
- which necessitates medical or surgical intervention within one year to preclude permanent impairment of a body function or permanent damage to a body structure.[16]



A ***permanent impairment*** is an irreversible impairment or damage to a body structure or function, excluding trivial impairment or damage.[17]

Also for purposes of risk classification, ***well characterized*** means the IVCT is well-established and well-recognized by the medical community, as evidenced by one or more of the following:

- Literature;
- Practice Guidelines;
- Consensus standards;
- Recognized standards of care;
- Technology in use for many years;
- Scientific publication by multiple sites;
- Wide recognition/adoption by the medical community; or
- Proficiency testing.

The risk classification for an IVCT is based upon the test's ***intended use***, which is the IVCT developer's stated purpose for the IVCT. If an individual IVCT has multiple intended uses, the IVCT will carry the risk classification of the highest-risk intended use.

[16] This definition draws upon the definition of "serious injury" in 21 C.F.R. § 803.3.
[17] This definition is identical to the definition of "permanent" in 21 C.F.R. § 803.3.

An accessory to an IVCT will be regulated on its own accord—it will not necessarily carry the risk classification of the parent IVCT to which it is an accessory. An ***accessory*** is a standalone product intended by its developer to be used in conjunction with one or more particular IVCTs to enable or assist the IVCT in performing its intended use.

5.1.1.Classification of New IVCTs

Each new IVCT will be classified into one of the three risk categories described above [high, moderate, low]. If a risk classification has already been established for the relevant IVCT type that risk classification will apply.

If a relevant risk classification does not exist, the developer will submit a proposed specific classification with proposed mitigations, if any, and a proposed test description. Prior to submitting a request for classification, the developer may request an informal discussion with the FDA.

In its request for classification, the developer will provide detailed information about the IVCT, including its intended use a description of the IVCT's composition, an explanation of the mechanism by which the IVCT works, and reasons for the recommended classification, as well as an explanation of how the proposed mitigations support the proposed classification. The FDA must reject or agree to the proposed classification within 60 calendar days. If FDA rejects the classification, it must provide an explanation of why the information and reasons submitted by the developer, as well as any valid scientific evidence submitted by the developer, did not support the classification. Rejection of a proposed classification will trigger appeal rights. An appeal can include a request for review by an advisory panel.[18]

Within 120 days FDA will publish a notice in the Federal Register announcing the classification and any applicable mitigations. .

Any IVCT or IVCT type classified under this process may be reclassified either on FDA's own initiative or in response to a petition for reclassification.

5.1.2.Reclassification

Stakeholders may request reclassification of an IVCT or the FDA may initiate reclassification proceedings. The reclassification process described in the proposed rule on medical device reclassifications published in 79 Fed. Reg. 16,252 (Mar. 25, 2014) will be the conceptual basis for the reclassification process, subject to the following changes:

- An IVCT may be reclassified solely because the IVCT is now well-characterized.
- An advisory panel will include stakeholders with knowledge of IVCTs, laboratory operations, and the use of IVCTs.

[18] Time frames for hearing an appeal will vary depending on whether a panel is used. An appeal does not preclude a reclassification request.

- The reclassification process will be effective upon completion of the classification process for existing IVCTs as set forth in Section 5.1.3.
- The requestor can immediately appeal a reclassification order without utilizing FDA processes for decision review.
- The decision to reclassify an IVCT from moderate-risk to high-risk will require the approval of the chief scientific officer or other member of senior management at the FDA center.

5.1.3. Downclassification

If the FDA determines that an IVCT should be down classified on its own initiative or at the request of another person, such as a laboratory, FDA will issue a notice in the Federal Register announcing its intent to down classify the IVCT without "mitigations" and provide a 60 day public comment period. For proposed down classifications with mitigations, the FDA will issue a notice in the Federal Register announcing its intent and provide a 90 day public comment period. If FDA has proposed to down classify with one or more mitigations, the Federal Register notice will contain the proposed mitigation(s). Within 60 days after the close of the public comment period, the FDA will consider the comments and issue a second notice in the Federal Register announcing its final decision, including any mitigation(s). When mitigations specify new product performance standards FDA will provide an appropriate grace period for products under FDA review or for IVCTs not yet under FDA review, but for which the mitigations are inconsistent with formal advice provided to the developer by FDA. This notice will amend the applicable classification regulation, as appropriate, and will constitute final agency action subject to judicial review.

In addition, FDA can use the 90-day process to add, modify or withdraw mitigations if warranted to maintain current classification if otherwise the IVCT would be upclassified.

5.1.4. Classification of Existing IVCTs

IVCTs currently on the market will be transitioned to the new risk classifications described above. Upon enactment, but prior to classification:

- Currently classified IVCTs subject to a premarket approval (PMA) will be considered high-risk IVCTs.
- Currently classified IVCTs subject to a 510(k) clearance will be considered moderate-risk IVCTs.
- Currently Exempt IVCTs will be considered low-risk IVCTs.

For initial classification of existing IVCTs, FDA will issue a Federal Register notice within 60 days of enactment identifying IVCTs that FDA determines are not appropriately classified and will request that stakeholders identify any IVCT for which (i) there is not an existing

classification, or (ii) the classification should be different than the deemed classification. There will be a 120-day public comment period for stakeholders to comment.

Within 180 days after the close of the comment period, FDA will submit to an advisory panel, and may group by type, any IVCT:

- For which the FDA believes the deemed classification should be changed;
- Identified by a stakeholder through public comment supported by a scientific rationale as an IVCT for which the deemed classification should be changed; or
- Identified by a stakeholder through public comment supported by scientific rationale as an IVCT for which there is not an existing classification.
- And any other IVCT FDA believes should be classified.

The advisory panel(s) will take public comments into consideration and may hold public meetings. Within 360 days, the advisory panel will provide recommendations on the classification for each IVCT, or IVCT type.

Within 180 days after the Advisory Panel makes its recommendations, the FDA will issue a Federal Register notice containing the final classifications for all IVCTs, or IVCT types, submitted to an advisory panel, with the exception of IVCTs that are proposed to be up-classified and subject to an additional comment process. If the FDA does not issue a final classification following the Advisory Panel's recommendation within the designated time period, the Advisory Panel recommendations will be presumed to be the final classification unless FDA has information sufficient to rebut that presumption. FDA will have 90 days following the 180-day deadline to publish a Federal Register notice containing the final classifications (taking into account the rebuttable presumption) for any remaining IVCTs that should have been classified within 180 days.

For IVCTs that are proposed to be up-classified, within 180 days after the Advisory Panel has made its recommendations, the FDA will issue a Federal Register notice proposing up-classification of the applicable IVCTs or IVCT types. The Federal Register notice will contain a public health justification that demonstrates a need for up-classification, and provide an opportunity for a 60 day public comment period. The decision to up-classify an IVCT will require the approval of the chief scientific officer or other member of senior management at the FDA center. After the close of the 60-day public comment period, FDA will have 90 days to issue a Federal Register notice with the final classifications for those IVCTs.

FDA will use only the Federal Register notice process to issue the classifications. For all other IVCTs, the deemed classification is considered final (subject to standard requests for reclassification pursuant to 5.1.2 or other agreed upon processes).

5.2. Premarket

5.2.1.Standard

The medical device premarket standard of safe and effective is conceptually inapplicable to IVCTs. An IVCT does not itself provide therapy and therefore cannot truly be measured as safe or unsafe. The critical question for an IVCT is whether the test is accurate. The rational measure of accuracy is through evaluation of the IVCT's analytical validity and clinical validity.

> ***The legal standard for marketing an IVCT is: Reasonable assurance of analytical validity and clinical validity for the intended use.***

For this purpose, ***analytical validity*** means the ability of a test to identify or measure the analyte or substance sought to be identified or measured, such as sensitivity, specificity, accuracy, precision, reference range, and reportable range. ***Clinical validity*** means the reliability and accuracy with which an IVCT identifies, measures, predicts, monitors, and/or assists in selecting treatment for, a disease or condition in humans, or characteristics related to an individual's clinical status, such as positive and negative predictive values. As noted above, the ***intended use*** of an IVCT is the IVCT developer's stated purpose of the IVCT.[19]

Reasonable assurance means the degree (type and amount) of competent and reliable evidence needed to demonstrate clinical validity and analytical validity. That degree of evidence will vary based upon the relevant:

- Population size;
- Disease state;
- Demographic representation;
- Limit of detection/analytical sensitivity;
- Disease severity;
- Type of use claim (*i.e.*, predictive, prognostic, diagnostic, treatment selection, screening);
- Availability and adequacy of warnings and restrictions;
- Clinical environment and use controls (*e.g.*, home use vs. office use);
- Technical and economic feasibility of additional studies;
- Impact of requiring additional studies on innovation and accuracy of test information;
- Past experience with similar IVCTs;
- Ease of use; and
- Other factors.

Analytical validity and clinical validity must be demonstrated by competent and reliable evidence. ***Competent and reliable evidence*** is evidence (i) which has been generated and evaluated by persons qualified by training and experience to do so, using procedures generally accepted by others in the profession, and (ii) for which it can fairly and responsibly be concluded by qualified experts that there is reasonable assurance of the accuracy and reliability of the results of a test for the intended use. Competent and reliable evidence may include:

- Peer reviewed literature;[20]

[19] Although clinical utility may be relevant for reimbursement purposes, it is not a criterion for marketing an IVCT.
[20] The underlying data is not required.

- Clinical guidelines;
- Expert opinion;
- Bench studies, including use of archived specimens;
- Past experience with similar products;
- Case studies;
- Clinical data;
- Consensus standards;
- Reference standards;
- Data registries;
- Post-market data; and
- Clinical trials.

It is presumed that clinical trials are not needed to demonstrate analytical validity or clinical validity unless the FDA center demonstrates in writing, based on scientific criteria, that other evidence is insufficient. Such writing must signed by the chief scientific officer or other member of senior management at the FDA center.

5.2.2. Approval with Confirmatory Post-Market Obligation

An IVCT is eligible to be marketed subject to confirmatory post-market obligations upon demonstration of a reasonable assurance of analytical validity and of probable clinical validity for the intended use if it is:

- an unmet need IVCT,
- a rare disease IVCT, or
- a moderate-risk IVCT that offers a clinically significant advantage over existing approved IVCTs, including the potential to facilitate patient access, reduce sample size, or more accessible specimen types.

Applications for AWPCO must fulfill all requirements associated with an application for approval of a moderate risk IVCT, except the application must provide valid scientific evidence supporting probable clinical validity for the intended use instead of a showing of reasonable assurance of clinical validity (RACV). The FDA will issue an order granting AWCPO and will include the applicant's agreement to meet a requirement to collect additional data to demonstrate RACV.

All required label and labeling for an IVCT with AWCPO shall bear the statement: "Approved with confirmatory post-market obligations."

A sponsor of an IVCT with confirmatory post-market obligations must comply with agreed upon post-market obligations, which may include reporting requirements.[21]

[21] The post-market obligations associated with an AWCPO may be modified or eliminated by mutual agreement of FDA and the sponsor.

The AWCPO approval will automatically lapse after a three year term, unless:

- A supplemental RACV application for approval demonstrating reasonable assurance of clinical validity is timely submitted by the sponsor and has not been denied.
- The applicant obtains an extension. The AWCPO term can be extended for up to one year by FDA if FDA believes an extension would be appropriate. The extension, by mutual agreement of FDA and the sponsor, may be for a time period different than one year.

AWCPO may be withdrawn by the FDA if the agency determines that, based on new evidence, the IVCT no longer provides a reasonable assurance of analytical validity, no longer provides probable clinical validity, or presents an unreasonable risk to human health. This will occur only after the FDA notifies the developer and there is an opportunity for an informal hearing.

If the sponsor of an IVCT with AWCPO submits a supplemental application, and FDA finds that there is not reasonable assurance of clinical validity, FDA will deny approval of the RACV supplement. Upon denial of the approval, the developer will be eligible to pursue the appeal process. [22] If the Center Director upholds the denial, the test will be an unapproved test and would be subject to enforcement action. The Center Director's decision may identify a timeframe for removal of the test from the market. The decision of the Center Director will be non-appealable, and constitutes final agency action subject to judicial review.

IVCTs with AWCPO that has not been withdrawn will automatically lapse on one of the following dates:

- The date that is three years after the date on which AWCPO was granted, if an extension has not been granted and if a supplemental RACV application was not submitted at least three months prior to this lapse date.
- The date specified in an extension order, if an extension was granted by FDA and the supplemental RACV application was not submitted at least three months prior to the lapse date specified in the extension order.
- The date on which FDA issues an order granting or denying approval of a supplemental RACV application, if such an application was submitted by the required date and if the sponsor does not appeal the order denying approval of the application.
- The date on which the Center Director issues a decision on an appeal of a denial of a supplemental RACV application, if such an application was submitted by the required date and if the sponsor appeals the original decision on the RACV application.

FDA may maintain a public database that lists IVCTs currently on the market which are subject to post-market obligations under this provision. This database can include the due date of such obligations and the status of such obligations, and shall be updated to reflect changes in IVCT status within ten (10) calendar days of the change.

[22] The sponsor can appeal that decision to the Center Director within 30 days of denial. The Center Director will decide the appeal not later than 45 days after a request is made, or, in the case of a person who requests an in-person meeting or teleconference, 30 days after such meeting or teleconference.

5.2.3. Submission and Review

The submission and review processes for IVCTs will vary by risk classification.

High-Risk. The developer of a high-risk IVCT must submit the IVCT to the FDA for affirmative approval prior to commercialization. The submission must establish a reasonable assurance of analytical validity and clinical validity for the intended use, and must include:

- Reports that reasonably establish information, published or known to or which should reasonably be known to the applicant, concerning investigations which have been made to show a reasonable assurance of analytical validity and clinical validity;
- A summary description of the IVCT, components, ingredients, and properties and of the principle or principles of performing the IVCT; and
- A declaration of conformity to quality requirements.

The FDA must approve or reject all submissions within 90 calendar days. No premarket inspection or manufacturing review will be required as a condition of approval, and the submission is not required to include detailed manufacturing information.[23] As with any situation, the FDA may inspect in ordinary course, but inspection is not a condition of approval.

Moderate-Risk. The developer of a moderate-risk IVCT must submit the IVCT to the FDA prior to commercialization. The submission must include evidence that establishes analytical validity and information to support the reasonable belief of clinical validity (*i.e.*, a summary clinical evidence report). See Addendum 2 for detailed overview of submission content for moderate-risk IVCTs.

The FDA may object, in writing, or request post-market reports on clinical validity, based on specific criteria, within 60 calendar days. If the FDA does not object within 60 calendar days, the IVCT is considered approved for commercialization. If the FDA requests additional information within the 60-day period but does not object based upon inadequate analytical data, the developer may commercialize the IVCT, but must submit the additional clinical data within one year or a longer period of time agreed to by the FDA and the developer. Failure to provide the requested additional information is grounds for withdrawal of the IVCT approval.

An improved third-party review process will be developed and made available for moderate-risk submissions.

Low-Risk. The developer of a low-risk IVCT must notify the FDA of any low-risk IVCT within 10 days following commercialization. The notification must include:

- The name of the IVCT;
- The intended use of the IVCT; and

[23] The declaration of conformity to quality requirements, and the Agency's authority to inspect, are sufficient to ensure manufacturing quality.

- A summary explanation of the IVCT.

Protocol Transfer. An approved/listed IVCT that is a laboratory test protocol may be transferred or sold to a third party, but the transferring or selling party must notify the FDA and quality obligations will be situation-dependent.

An approved/listed IVCT that is a laboratory test protocol can be shared with multiple laboratory operators within a corporate family[24] without further premarket review or notification.

5.3. Modifications

Clarity and efficiency are critical with regard to the regulatory requirements that apply when a marketed IVCT is modified. It is important that the regulatory scheme does not unduly limit modifications to IVCTs because modifications need to be made frequently to improve test performance, address quickly evolving clinical needs, and enhance efficiency.[25]

FDA and CMS has distinct jurisdictions with regard to modifications. FDA has jurisdiction over activities used in the design, development, and validation of an IVCT (finished product or protocol).[26] Whereas, CMS has jurisdiction over activities in the implementation and use of the IVCT (lab operations).[27]

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[24] This refers to an entity that controls, is controlled by, or is under common control with, the developer of the laboratory test protocol.

[25] Examples of modifications that are common include:
- Extending specimen stability to enable transportation of a specimen from other healthcare facilities.
- Adding other specimen types for testing.
- Using alternative specimen collection containers.
- Modifying processing steps in the testing process, such as removing the use of xylene or extending an incubation time.

A CLIA laboratory is required to verify that modifications do not change the intended use of the test.

[26] Activities within FDA jurisdiction include:
- IVCT Design, e.g., establishing intended use(s), creation of analytically and clinically relevant performance specifications, determination or identification of , instrumentation, software, reagents
- IVCT Development, e.g., creating actual IVCT design, developing use instructions, and implementing performance specifications (based on design inputs and design outputs),
- Verification and Validation activities for design outputs
- Manufacturing of the IVCT, including manufacturing reagents, components, instruments, software
- Creation of IVCT label or instructions for IVCT utilization, including, as applicable, FDA required to patient related instructions
- Creation of adequate instructions for use for a finished product
- Modifications to the design or manufacture of the IVCT
- Creation of specifications for materials needed to implement or use an IVCT

Some examples of activities under FDCA include:

- creation of design inputs and outputs
- assessing materials for use in manufacturing a finished product
- addition of new intended use
- changes in design related to analytical or clinical validity

[27] Examples of lab operations under CLIA include:
- Implementation of changes to an IVCT to allow the clinical evaluation of a single patient's sample(s)

The regulatory requirements applicable to IVCT modifications will be based on the risk profile of the modified IVCT and the impact of the modification. Modification submissions will be required if a modification changes the intended use, does not meet required mitigations, there is a reasonable probability or a meaningful increase in risk to the patient or user, or the analytical or clinical performance for the intended uses is demonstrated to be outside of the approved analytical or clinical performance claims for the intended use. Addendum 3 provides detailed review of instances that trigger submissions to the FDA regarding the modification.

Modification of a High-Risk IVCT. A modification to a high-risk IVCT must be submitted to the FDA for review if:

- The modification has a meaningful clinical impact (*i.e.*, changes diagnosis or therapy delivered to patient), post-verification and -validation;[28] or
- The modification changes the intended use of the IVCT and the new intended use is a high-risk use or a moderate-risk use.

If the modification changes the intended use of the IVCT to a new intended use that is a moderate-risk use, the submission is reviewed in the same manner as a new moderate-risk IVCT. Other modifications subject to submission will be reviewed in the same manner as a new high-risk IVCT.

Modification of a Moderate-Risk IVCT. A modification to a moderate-risk IVCT must be submitted to the FDA for review if:

- The modification has a meaningful clinical impact (*i.e.*, changes diagnosis or therapy delivered to patient), post-verification and -validation; or
- The modification changes the intended use of the IVCT and the new intended use is a high-risk use or a moderate-risk use.

If the modification changes the intended use of the IVCT to a new intended use that is a high-risk use, the submission is reviewed in the same manner as a new high-risk IVCT. Other modifications subject to submission will be reviewed in the same manner as a new moderate-risk IVCT.

- Changing parameters on an open instrument system to allow a lab to verify analytical performance specifications of an IVCT
- Choosing appropriate quality control materials for use with the IVCT
- Troubleshooting/investigating IVCT performance problems
- Choosing/preparing reagents to meet specifications of an IVCT
- Operation/implementation of a laboratory test protocol within the approved range of specifications in the protocol
- Creating/modifying processes (e.g., SOPs) used for implementation of an IVCT
- Maintenance of equipment

[28] Examples of modifications that would not be subject to review, *if validated and verified as not having a meaningful clinical impact*, include: (i) a change in specimen type; (ii) use of a specimen storage temperature that varies from the manufacturer's instructions; (iii) a change from a manual process to an automated process; (iv) a change in specimen collection method; (v) a change in control material; (vi) change in specimen stability; and (vii) a change in calibrator used. This approach is intended to focus the FDA's limited and valuable resources on high-risk products and modifications that change intended use. It is important to bear in mind that these IVCTs remain under FDA oversight (*i.e.*, subject to quality and post-market requirements) even when not submitted for review. A more expansive submission requirement would vastly increase the number of submissions and divert FDA resources away from review of meaningful and innovative new IVCTs.

Modification of a Low-Risk IVCT. A modification to a low-risk IVCT is not required to be submitted for FDA review unless the modification changes the risk classification of the IVCT. If the modification does change the risk classification of the IVCT, the IVCT must be submitted as a new moderate-risk or high-risk IVCT, as applicable.

For purposes of modifications, a change in intended use is a change in the type of analysis (*e.g.*, qualitative vs. quantitative); the purpose of the assay (*e.g.*, a change from screening to diagnosis); or the target disease or condition.

The entity that makes a change to the design of an IVCT becomes a developer and, therefore, is under FDA jurisdiction regardless of if the change triggers a submission. The entity that modifies the IVCT is responsible for determining, based on its quality system, whether the modification is required to be submitted. Agency review of any modification is limited to the modification; review does not extend to other aspects of the IVCT being marketed.[29]

The developer must document any change to its IVCT, even if the change does not meet the modification standard above. If a laboratory operator changes an IVCT in a way that does not reach the modification standard above, the laboratory operator must comply with quality and documentation requirements under CLIA, but that change is not subject to any FDA-regulated documentation.

It is important that the regulatory scheme for modifications permits laboratory-industry collaborations in order to evaluate the clinical impact of a change to an industry-manufactured test kit. If a modified test is used for non-patient care purposes (*i.e.*, research), no modification requirements or off-label restrictions are triggered.

5.4. Labeling

Finished products will comply with labeling and label requirements relevant to IVCTs. The conceptual basis for such requirements will be 21 C.F.R. § 809.10.

A laboratory test protocol is subject to core labeling requirements. A "label" (as defined in the FD&C Act) is not required to be affixed to the physical elements of an IVCT that is not distributed to another facility or a third party. The developer may satisfy the labeling obligation by maintaining and making generally available to users and health care professionals an

[29] For example, if an IVCT for condition A is modified to add an intended use for the diagnosis of condition B, review is limited to the IVCT's clinical and analytical validity with respect to condition B, and the FDA cannot use the modification as a means to reevaluate the IVCT with respect to condition A.

electronic copy of the label.[30] Legitimate scientific or medical exchanges or discussions will not be labeling or constitute a change in intended use.

The patient test report or an interpretation of test results is regulated exclusively under CLIA or state practice of medicine rules and is outside the scope of FDA jurisdiction. These reports will not be deemed a "label" or "labeling" under the FD&C Act.

5.5. Quality

Quality requirements for test development will generally track current FDA quality requirements with the following changes:

- A clear line will be drawn to clarify that laboratory operations are not subject to FDA quality requirements. Quality requirements will be limited to test development activities, including the production of finished product for distribution to other facilities or third parties.
- Finished products and laboratory test protocols will be subject to design controls.
- Component and raw material suppliers will be subject to supplier controls rather than direct FDA oversight.
- Identifier requirements similar to the unique device identifier (UDI) system will apply to a finished product, but will not apply to laboratory test protocols.
- Modernized CLIA obligations, not FDA quality system requirements, will apply to laboratory operations, but will be harmonized with FDA requirements as appropriate.
- The IVCT developer will be responsible for post-market requirements.

Appendix A sets out more specific proposed quality requirements, which will need to be translated to legislation.

5.6. Post-Market

5.6.1.Event Reporting

[30] Laboratory testing directories or catalogues generally make the following information available to health care professionals regarding tests performed, whether an IVCT protocol or an IVCT finished product is being used to perform patient testing:

- Proprietary name and established name of the test
- Intended use or uses of the test
- Summary and explanation of the test
- Specimen collection and preparation
    - Special precautions including special preparation of the patient
    - Preservatives, etc. to maintain specimen integrity
    - Known interfering substances
    - Recommended specimen storage, handling, shipping, and maintenance
- Results
- Limitations of the procedure
    - Known extrinsic factors or limiting substances
- Expected values
- Specific performance characteristics
    - Accuracy, precision, specificity, and sensitivity
- Bibliography

The developer of an IVCT must report to the FDA, in the manner described below, any adverse event known to the developer. An ***adverse event*** is:

- any death or serious injury reasonably believed to have been caused by an IVCT error, and
- any IVCT error for which, if the error were to reoccur, the IVCT error has a reasonable probability (*i.e.*, more than a remote possibility, taking into account the probability of recurrence, existing safeguards, and the probability of resulting harm) of causing death or serious injury.[31]

IVCT developers must establish and maintain adverse event files that clearly identify all adverse events and facilitate timely access. For this purpose, adverse event files are written or electronic files maintained by IVCT developers that may incorporate references to other information (*e.g.*, medical records, patient files, engineering reports), in lieu of copying and maintaining duplicates in this file. Adverse event files must contain:

- Information in the IVCT developer's possession or references to information related to the adverse event, including all documentation of the developer's deliberations and decision-making processes used to determine if an IVCT error was reportable; and
- Copies of all required adverse event submissions, and other information related to reported events.

The developer must submit an event-specific report within five (5) calendar days for any adverse event known to the developer that involves actual patient death. The developer must submit an event-specific report within fifteen (15) calendar days for any adverse event that presents an imminent threat to public health. The event-specific report will include information similar to the information required in the current FDA Form 3500A, including:

- Patient information;
- Adverse event information;
- Suspect test information;

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An ***IVCT error*** is a clinically significant failure of an IVCT to meet its performance specifications or otherwise perform as intended. An error related to laboratory operations is not an IVCT error. User errors and human factor issues are not reportable, but rather will be an input into the entity's quality systems pursuant to CLIA.

Cause means that an IVCT error is the primary factor in a death or serious injury within one year of the IVCT error related to that specific patient or user.

A ***serious injury*** means an injury or illness that:

- Is life-threatening,
- Results in permanent impairment of a body function or permanent damage to a body structure, or
- Necessitates medical or surgical intervention to preclude permanent impairment of a body function or permanent damage to a body structure.

Permanent means irreversible impairment or damage to a body structure or function, excluding trivial impairment or damage.

- Reporter information;
- Test developer information; and
- Lab operator information.

The developer must also submit a quarterly summary report for all adverse events known to the developer.[32] The summary report will include:

- Number and type of covered events;
- Trend information regarding covered events;
- Patient impact summaries; and
- Any newly identified issues or problems.

A quarterly report is not required for any quarter in which no adverse events occur. The FDA may request event-specific information.

The test developer is responsible for adverse event reporting. A laboratory operator, healthcare provider, or user with knowledge of an adverse event may also report.

5.6.2. Correction or Removal Actions

The FDA will mandate information necessary in IVCT corrections and removals and in user communications. In addition, class I classification timeframe will apply to all corrections and removals (30 days).

Developer or other responsible parties will identify and initiate voluntary correction or removal actions. The developer or other responsible party will submit the voluntary correction or removal information to the FDA within 7 days of the first action.[33]

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[32] Similar trend-based reporting is utilized in the pharmaceutical industry. These reports will be based on investigated events.

[33] Submitted information will include:

a. IVCT name, ID or model number, serial number, UDI, etc.
b. Name, address, registration number of correcting or removing developer or other responsible party and contact information.
c. Copy of customer notification.
d. Description of the problem, including:
    i. How the problem was discovered,
    ii. Errors seen in the field, and
    iii. Estimated number of customers (i.e., tests) impacted.
e. A status and summary of the developer or other responsible party's internal investigation.
f. Health hazard evaluation, based on available information, including:
    i. A description of the bias magnitude, direction, and frequency, and any special conditions or sample types that it occurs with.
    ii. A description of whether quality controls will detect the error.
    iii. Information sufficient to determine severity of harm.
i. Number of adverse event reports related to the problem.
j. IVCT labeling, particularly instructions for use.
k. List of consignees.

Upon receipt of voluntary correction and removal information, the FDA will assign a unique correction or removal identifier and provide that to the developer or other responsible party within 7 days. All subsequent communications will include the unique correction or removal identifier, including all communications to the IVCT user.

Correction or removal will be formally classified within 30 days. After the developer notifies the FDA that it has completed the correction or removal, the FDA will have 45 days to issue a letter closing the correction or removal or stating the reasons it cannot close the correction or removal

If FDA determines an additional notification is needed for public health reasons, the FDA may issue a statement that will include language clarifying that it is intended to inform patients and health care providers that this is not a second correction or removal and that this is an agency process for classifying an existing correction or removal.

When it is necessary to have communication to the user, the developer or other responsible party's communication must include, as applicable:

- Unique Correction or Removal Identifier (if assigned)
- Information sufficient to identify the corrected or removed IVCT
- Description of the problem with the IVCT, including extent of the problem (e.g., extent of measurement bias, percent increase in imprecision, percentage of IVCTs affected, etc.)
- Description of the potential risks to patients or the public due to the problem, including whether there were associated injuries or deaths
- Instructions to the user on appropriate actions to take
- Contact information to obtain additional information from the developer or other responsible party

5.6.3.Post-Market Studies

No post-market studies are required, except as required by the approval authorization processes described above or as necessitated by legitimate public health demands following consultation with the IVCT developer.

5.6.4.Annual Report

No annual reporting is required for any IVCT. Data typically included in annual reports is available at the FDA's legitimate, test-specific request or upon inspection.

5.6.5.CAPA

Field experience will be an input into CAPA systems and design systems pursuant to the developer's quality system.

6. Regulatory Requirements for Laboratory Operations

As discussed above, the activities involved in performing an IVCT in a laboratory environment are distinct from the activities involved in developing that IVCT, and accordingly, different regulatory requirements should apply to laboratory operations.

6.1. Modernizing CLIA

Lab operations will continue to be subject to CLIA requirements, but CLIA standards will be updated to reflect current advances in diagnostic testing and account for future advancement of the clinical laboratory testing industry. Changes will also be made to clearly delineate the activities that will be regulated by FDA from those activities that will continue to be regulated by CMS under CLIA. Current CLIA standards will be updated to align with the more stringent accreditation standards of the College of American Pathologists (CAP), which has updated its requirements to address advances in clinical laboratory testing. For example, the CAP checklists have been enhanced over the past several years to include specific requirements to ensure enhanced quality standards for each of the specialty areas identified below.

Specifically, the following changes will be made to CLIA:

1. **Expand the CLIA certificate specialties/sub-specialties to include:**
    - Molecular Pathology, Molecular Microbiology, Biochemical Genetics, Flow Cytometry.
    - A certificate sub-category for laboratories that implement IVCT laboratory protocols.
2. **Update the CLIA standards for the new specialties/sub-specialties.** The CAP checklists can be the source of the new standards.
3. **Develop new CLIA standards for genetic testing** (*e.g.*, molecular pathology, molecular microbiology, biochemical genetics), and update existing cytogenetics standards and flow cytometry. Update microbiology standards to reflect the use of molecular methodologies.
4. **Add appropriate references to the new regulatory framework** for the design, development, and validation of IVCTs regulated by FDA and the enhanced CLIA standards and requirements for implementing IVCT laboratory protocols through laboratory operations.
5. **Clarify that modifications of IVCTs** will be regulated by FDA, whether a submission is required or not, and that when an FDA submission is not required (*e.g.*, a low risk modification), validation of such modification will be governed by the FDA validation standard of reasonable assurance of analytical validity and clinical validity, not by CLIA. CLIA will continue to govern verification of such modifications and their implementation through SOPs. Changes will clarify that FDA validation and CLIA verification of specimen stability and specimen type modifications apply only to the performance specifications of the modification (*i.e.*, precision, accuracy, reportable range), and not to the performance characteristics of the entire assay.
6. **Enhance quality requirements:**
    - The CLIA standard for complaint investigation will be expanded to address reporting of adverse events related to the use of a finished product. The laboratory

quality management system must include a program to identify and evaluate errors, incidents, and other problems that may interfere with patient care services. The laboratory must document investigation and resolution of these problems. The laboratory must perform a root cause analysis of any unexpected event causing death or serious injury or risk thereof (including "near misses" and sentinel events). The laboratory must have a procedure to report IVCT related adverse patient events, as required by the FDA. The FDA definition (above) of an adverse event report will be used. CAP checklists will be a source of the updated standards.

- The CLIA standards will be expanded to include criteria for purchasing controls applicable to laboratory operations, which is especially important for purchase of materials to be used in tests performed using an IVCT laboratory protocol. A supplier qualification program would be included in the new standard.
- CLIA quality requirements for preparation of reagents for use in the CLIA laboratory will be enhanced to ensure consistent reagent preparation and quality control of the reagent. These enhanced requirements will only apply to reagents prepared by the individual CLIA facility that will use them.

7. **Enhance requirements for Laboratory Computer Systems:**
    - The CLIA standards for laboratory computer systems, including security standards, data integrity, auto-verification standards, and standards for internal controls of software modifications will be enhanced. Laboratory information systems and other computer system programs are commonly used in the CLIA laboratory. The CAP checklist will be the source of the new standards.
8. **Harmonization of terminology used across the regulatory agencies:**
    - CLIA and FDA terminology, such the terms validation and verification, will be updated to use common definitions that can be applied consistently by both agencies.

7. Platforms and Special Categories

7.1. Platforms

A ***platform*** is an article comprised of hardware, and in some cases software, that is intended by its developer to be used with *in vitro* clinical tests to generate a clinical test result. A platform may be compatible with more than one specific assay and those assays may range from low-risk to high-risk.[34]

Platforms are classified independently of the assays they run, as low-risk. Prior to marketing a platform, the platform developer must establish that the platform meets its performance specifications and is capable of performing intended IVCTs to labeled levels of analytical

[34] Although platforms may be IVCTs, platforms have distinct characteristics that should be accounted for in setting the applicable regulatory requirements. With regard to validity, the individual assays to be performed on the platform will be subject to premarket requirements and will be validated in combination with the platform.

validity. Individual IVCT performed using a platform is classified according their intended uses and independently of the platform.

The developer of a platform may not make claims of clinical validity on the platform alone.

7.2. Investigational IVCTs

An investigational use only (IUO) IVCT is outside the scope of FDA jurisdiction unless it presents a significant risk. If the IUO IVCT presents a significant risk, FDA will exercise oversight through a process similar to an IDE. The IDE process will be streamlined and improved. Developers will be allowed to use de-identified samples without informed consent.

A significant risk IVCT means an investigational test that (i) is for a use of substantial importance in identifying, measuring, predicting, monitoring, or assisting in selection of treatment for, an impairment of human health, and presents a potential for serious risk to the health of a subject, or (ii) otherwise presents a potential for serious risk to the health of a subject.

At any time, the FDA may prohibit the sponsor of an investigation from conducting the investigation (referred to as a "clinical hold") if the FDA makes a determination that the in vitro clinical test involved presents an unreasonable risk to the safety of the persons who are the subject of a clinical investigation or there is credible evidence that investigator misconduct or sponsor non-compliance with the requirements set forth for investigational IVCTs present an unreasonable risk to the safety of the persons who are the subjects for the clinical investigation. A sponsor may request removal of a clinical hold.

7.3. Research Use Only

A ***research use only test*** is an IVCT that is in the laboratory research phase of development, and is not an IVCT.[35] Therefore, a research use only test is outside the scope of FDA and CMS jurisdiction and is not subject to the regulatory requirements outlined in this proposal.

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[35] This definition is based on the FDA's November 25, 2013 guidance on Distribution of *In Vitro* Diagnostic Products Labeled for Research Use Only or Investigational Use Only. That guidance provides:

> An RUO product is an IVD product that is in the laboratory research phase of development and is being shipped or delivered for an investigation that is not subject to part 812. During the research phase of development, the focus of manufacturer-initiated studies is typically to evaluate design, limited-scale performance, and issues such as usability of the test. Some examples of products FDA would consider to be in this research phase include:
>
> - Tests that are in development to identify test kit methodology, necessary components, and analytes to be measured.
> - Instrumentation, software, or other electrical/mechanical components under development to determine correct settings, subcomponents, subassemblies, basic operational characteristics, and possible use methods.
> - Reagents under development to determine production methods, purification levels, packaging needs, shelf life, storage conditions, etc.
>
> FDA also recognizes that there are certain products, such as instruments, systems, and reagents that are labeled for research use only and intended for use in the conduct of non-clinical laboratory research with goals other than the development of a commercial IVD product, i.e., these products are used to carry out research and are not themselves the object of the research. These include products intended for use in discovering and developing medical knowledge

7.4. Rare Disease

An IVCT qualifies as an orphan IVCT if the Secretary finds that:

The IVCT is intended for a disease or condition with an incidence of 8,000 or fewer or a prevalence of 50,000 or fewer in the United States, except for IVCTs intended for screening of asymptomatic patients or predicting occurrence of a future disease or condition in asymptomatic patients.

Orphan IVCTs are subject to special premarket requirements. The developer of an orphan IVCT must notify the FDA of its intent to market the IVCT and must submit evidence of analytical validity and a conceptual or theoretical basis for clinical validity. The FDA may object to the marketing of the IVCT within 30 calendar days. All objections must be documented in writing and based on valid scientific concerns. If the FDA does not object within 30 calendar days, the IVCT may be marketed.

Post-market, the developer of an orphan IVCT must collect clinical validity data of the type relevant to the appropriate risk classification of the IVCT. This obligation continues until the developer has collected the level of evidence necessary to demonstrate clinical validity for that risk classification. The developer will report the results of the collected data upon completion, but if completion takes more than one year, the information will be reported annually.

The developer of an orphan IVCT may advertise or promote the test's availability following notification to the FDA as described above, but in doing so, the developer must disclose the fact that actual clinical validity has not been shown. This disclosure obligation terminates once sufficient post-market information has been collected to demonstrate clinical validity.

7.5. Emergency

An ***emergency use IVCT*** is an IVCT that identifies, measures, predicts, monitors, or assists in selecting treatment for, a serious or life-threatening disease or disorder that is an imminent threat to public health, including a public health emergency declaration pursuant to section 319 of the Public Health Service Act and similar declarations by other federal and international public health authorities.

Emergency use IVCTs are subject to special premarket requirements. The developer of an emergency use IVCT must notify the FDA of its intent to market the IVCT and must submit evidence of analytical validity and a conceptual or theoretical basis for clinical validity. The FDA may object to the marketing of the IVCT within 10 calendar days. All objections must be

related to human disease and conditions. For example, instruments and reagents intended for use in research attempting to isolate a gene linked with a particular disease may be labeled for research use only when such instruments and reagents are not intended to produce results for clinical use.

documented in writing and based on valid scientific concerns. If the FDA does not object within 10 calendar days, the IVCT may be marketed.

Post-market, the developer of an emergency use IVCT must collect clinical validity data of the type relevant to the appropriate risk classification of the IVCT. This obligation continues until the developer has collected the level of evidence necessary to demonstrate clinical validity. The developer will report the results of the collected data upon completion, but if completion takes more than one year, the information will be reported annually.

The developer of an emergency use IVCT may advertise or promote the test's availability following notification to the FDA as described above, but in doing so, the developer must disclose the fact that actual clinical validity has not been shown. This disclosure obligation terminates once sufficient post-market information has been collected to demonstrate clinical validity. A manufacturer may consult with the FDA for continued marketing and distribution of the product after termination if the above conditions continue to be satisfied.

Revisions to 21 USC 360bbb-3b is necessary to include IVCTs.

7.6. Unmet Need

An ***unmet need IVCT*** is an IVCT, other than an emergency use IVCT or a rare disease IVCT, that is intended to identify, measure, predict, monitor, or assist in selecting treatment for, a serious or life-threatening disease or disorder, for which there is no existing IVCT with the same intended use and for which the IVCT could lead to a meaningful improvement in treatment or therapy. An unmet need IVCT will be regulated as a moderate-risk IVCT.

7.7. Future Technologies

Any regulatory scheme must have the flexibility needed to accommodate future innovative technologies.

8. Preemption

No State or political subdivision may establish or continue in effect any requirement related to IVCTs which is different from, or in addition to, any requirement in this proposal[36]; provided however, the practice of medicine, as described in this proposal, may be regulated by the States. This preemption extends to both IVCT development requirements regulated by the FDA and laboratory operation requirements regulated by CMS under CLIA.

States are not preempted from:

- Licensing[37]; and

[36] "Requirements in effect" or other approaches will be considered to avoid gaps during transition.
[37] Licensure requirements cannot include conditions of licensure that are different than CLIA.

- Laws of general applicability (*e.g.*, zoning, environmental requirements, labor laws, general business registration).

CMS may delegate (in a non-duplicative manner) the following functions to a State or political subdivision or a deemed CLIA accreditation agency, provided that the delegatee may not establish requirements that are different from, or in addition to, any requirements in this proposal:

- Inspections; and.
- Certification or accreditation.

9. Fees

User fees will not be the primary funding source for the new regulatory structure. User fees should track more closely the funding ratio for devices (currently approximately 25%) rather than drugs (currently approximately 80%). Different user fee amounts should apply to high-risk submissions and moderate-risk submissions. A small-business reduction in user fees will be available. FDA will agree to mutually acceptable performance goals as part of the user fee process.

Registration fees will be corporate-entity level, not at the individual-facility level. A listing requirement will apply at the individual-facility level, but will not carry a fee.

CLIA fees will be credited against FDA fees.

10. Inspections, Penalties, and Enforcement

10.1. General Inspection and Enforcement Provisions

The FDA and CMS may use agency inspectors or FDA or CMS certified third party inspectors to conduct inspections of those entities regulated under their respective jurisdictions and will conduct inspections in accordance with the applicable agency's regulations, policies, procedures, and guidelines.

FDA inspectors shall conduct inspections of IVCT developers' facilities that may include diagnostic laboratories (CLIA and non-CLIA) that have developed IVCT products or protocols for purposes of assessing the inspected entity's compliance with regulations applicable activities that are under the jurisdiction of the FDA.CLIA focused inspections of CLIA certified facilities will be conducted by CMS certified inspectors. Inspections will be conducted under the [38]jurisdiction of CMS and its applicable regulations.

[38] In conducting an inspection, a hybrid inspector must:

a. Identify the purpose and scope of the inspection (CLIA or FDA focused) at its outset or in any pre-announcement of a planned inspection in accordance with the regulations, policies, procedures and guidelines of the applicable regulatory agency under which the inspection is to be conducted.
b. Conduct the inspection in accordance with its announced purpose as if the hybrid inspector were conducting an inspection solely as a CLIA or FDA inspector.

FDA and CMS may, by written inter-agency agreement (or memorandum of understanding), develop a program to educate, train and certify inspectors as duly qualified to conduct both FDA and CLIA directed inspections on behalf of the applicable agencies. These inspectors will be termed "hybrid" inspectors.

Any inspector can notify the appropriate agency of suspected regulatory deficiencies regarding an inspected facility's activities.

10.2. Withdraw and Notification

The FDA will have the authority (acting through the Center director or chief science officer) to withdraw approval of an IVCT if:

- based on competent and reliable evidence, the IVCT has been determined to cause serious or life threatening harm when used as intended, and its continued use for its intended purpose will cause death or serious harm;
- the submission included material false statements;
- the IVCT quality systems are in violation (after notice and an opportunity to correct); or
- the IVCT labeling is materially false or misleading and is not corrected.

In addition, FDA will have the authority to compel notification to affected users if an IVCT presents an unreasonable risk of death or serious injury when used as intended or presents an imminent threat to public health.

Likewise, FDA will have the authority to mandate a removal or corrective action if FDA finds that the IVCT presents an unreasonable risk of death or severe adverse health consequences.

Streamlined appeal processes will be available to the developer to help ensure that patients are not unnecessarily deprived of access to an IVCT.

11. Transition and Grandfathering

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c. Where an entity is both an IVCT developer and a CLIA certified laboratory, and when for purposes of reducing the number of inspections a hybrid inspector wishes to conduct both a CLIA inspection and an FDA inspection during a single visit, the hybrid inspector shall notify the facility according to section 5 (a) (i) that both a CLIA and FDA inspection shall occur. In conducting such an inspection, the inspector shall:
    i. Maintain a clear distinction between the CLIA laboratory functions and FDA regulated functions; and
    ii. Conduct each phase of the inspection separately so that the facility being inspected has due notice of the scope of the inspection as it is being performed; and
        iii. Shall not extend the FDA inspection into CLIA laboratory operations, but where the CLIA inspection raises an issue within the FDA's jurisdiction, the hybrid inspector must follow the process set forth in section 5 (a) (iv) below.

d. When a CLIA focused inspection raises an issue within the FDA's jurisdiction, the hybrid inspector shall notify the CLIA laboratory of the issue and, at the discretion of the inspector, the FDA may also be notified of the FDA related issue.

The FDA shall determine whether any such notice from any inspector raises an issue within the FDA's jurisdiction that would warrant other action under existing statute or regulation.

11.1. Grandfathering

Laboratory tests previously marketed as LDTs will be grandfathered into the IVCT construct. LDTs offered three months prior to the date of enactment would be exempt from premarket review/submission requirements and from compliance with design controls.

Grandfathered IVCTs could stay on the market without an additional IVCT approval unless (1) the provisions of section 1 or 2 are triggered as outlined in Addendum 1; or (2) a modification is made that triggers the requirement for submission to FDA.

Grandfathered tests would be subject to the following requirements as set forth in this section:

- Quality systems (other than design controls)
- Post-market requirements
- Listing

11.2.Time Frames

Revised CLIA regulations will be finalized within two years after enactment of the statute. The revised CLIA regulations will be effective two years after finalization.

FDA regulations on design controls, quality requirements, and post-market obligations will be finalized within two years after enactment of the statute. The FDA regulations on design controls, quality requirements, and post-market obligations will be effective two years after finalization.

FDA regulations on submissions will be finalized within two years after enactment of the statute. The FDA regulations on submissions will be effective one year after finalization for manufacturers. A delayed effective date of two years after finalization will apply to laboratories.

11.3.Laboratory Operations

No FDA requirements apply to laboratory operation activities at any time. Laboratory operation activities will be regulated under current CLIA requirements (and related state requirements) prior to the effective date of the new CLIA regulations. Laboratory operation activities will be regulated under the new CLIA requirements after the effective date of the new CLIA regulations.

11.4.Test Development Activities

11.4.1.Design Controls

With regard to manufacturers:

- IVCTs introduced prior to enactment are subject to 21 CFR Part 820. IVCTs introduced after enactment but prior to finalization of the regulations are subject to 21 CFR Part 820.

- IVCTs introduced after finalization of the regulations, but before the effective date of the regulations, may comply with either (i) 21 CFR Part 820, or (ii) the new FDA design controls.
- IVCTs introduced after the effective date of the regulations must comply with the new FDA design controls.

With regard to laboratories:

- IVCTs introduced prior to enactment are not subject to FDA design controls; they are subject to any existing CLIA or state requirements.
- IVCTs introduced after enactment but prior to finalization of the regulations are not subject to FDA design controls; they are subject to any existing CLIA or state requirements. For IVCTs introduced after finalization of the regulations, but before the effective date of the regulations, laboratories may choose to comply with either (i) any existing CLIA or state requirements, or (ii) the new FDA design controls. If a laboratory chooses to comply with the new FDA design controls, CLIA and state design controls are preempted.
- IVCTs introduced after the effective date of the regulations must comply with the new FDA design controls.

11.4.2.FDA Quality Systems (Other Than Design Controls)

With regard to manufacturers:

- Prior to finalization of the regulations, manufacturers must comply with 21 CFR Part 820. This applies to all of the manufacturer's IVCTs regardless of when they were introduced.
- After finalization of the regulations, but prior to the effective date of the regulations, manufacturers may comply with either (i) 21 CFR Part 820, or (ii) the new FDA quality requirements. This applies to all of the manufacturer's IVCTs regardless of when they were introduced.
- After the effective date of the regulations, manufacturers must comply with the new FDA quality requirements. This applies to all of the manufacturer's IVCTs regardless of when they were introduced.

With regard to laboratories:

- Prior to finalization of the new FDA quality regulations, laboratories must comply with any CLIA and state quality requirements. No FDA requirements apply. This applies to all of the laboratory's IVCTs regardless of when they were introduced.
- After finalization of the regulations, but prior to the effective date of the regulations, laboratories may comply with either (i) any CLIA and state quality requirements, or (ii) the new FDA quality requirements. This applies to all of the laboratory's IVCTs regardless of when they were introduced. If a laboratory chooses to comply with the new FDA quality requirements, CLIA and state quality requirements are preempted.

- After the effective date of the regulations, laboratories must comply with the new FDA quality requirements. This applies to all of the laboratory's IVCTs regardless of when they were introduced.

11.4.3.FDA Post-Market Requirements

With regard to manufacturers:

- Prior to finalization of the regulations, manufacturers must comply with 21 CFR Part 820 and 803 post-market obligations for all of its IVCTs regardless of when they were introduced.
- After finalization of the regulations, but prior to the effective date of the regulations, manufacturers may comply with either (i) 21 CFR Part 820 and 803, or (ii) the new FDA post-market requirements. This applies to all of the manufacturer's IVCTs regardless of when they were introduced.
  After the effective date of the regulations, manufacturers must comply with the new FDA post-market requirements. This applies to all of the manufacturer's IVCTs regardless of when they were introduced.

With regard to laboratories:

- Prior to finalization of the regulations, laboratories must comply with any CLIA and state post-market obligations for all of its IVCTs regardless of when they were introduced.
- After finalization of the regulations, but prior to the effective date of the regulations, laboratories may comply with either (i) any CLIA and state post-market obligations, or (ii) the new FDA post-market requirements. If a laboratory chooses to comply with the new FDA post-market requirements, CLIA and state post-market requirements are preempted. This applies to all of the laboratory's IVCTs regardless of when they were introduced.
- After the effective date of the regulations, laboratories must comply with the new FDA post-market requirements. This applies to all of the laboratory's IVCTs regardless of when they were introduced.

11.4.4.Listing

With regard to manufacturers, within 180 days after enactment manufacturers must list any existing IVCTs not already listed (minimum information to identify the IVCT). All IVCTs must be listed annually thereafter.

With regard to laboratories, within 180 days after enactment laboratories must list all existing IVCTs (minimum information to identify the IVCT). All IVCTs must be listed annually thereafter.[39]

[39] The listing requirements in this subsection are not considered the listing of a medical device under section 510(j) of the FD&C Act or 21 C.F.R. Part 807. Physicians employed by IVCT-developing laboratories remain outside the scope of Sunshine Act reporting requirements.

11.4.5.Submissions

With regard to manufacturers:

- For IVCTs introduced prior to the effective date of the regulations (*i.e.*, 3 years after enactment), manufacturers must comply with existing FDA submission and approval/clearance requirements. The new submission process is not available prior to the effective date of the regulations (*i.e.*, 3 years after enactment).
- For IVCTs introduced after the effective date of the regulations (*i.e.*, 3 years after enactment), manufacturers must use the new submission process.

With regard to laboratories:

- For IVCTs introduced prior to enactment, no submission obligations will apply to such IVCTs prior to the delayed effective date of the regulations (*i.e.*, 4 years after enactment). After the delayed effective date of the regulations (*i.e.*, 4 years after enactment), an informational notification to FDA containing a summary of available analytical and clinical validity data will be required for high-risk IVCTs that have not been approved by New York State or FDA. Such notification will be less detailed than a full submission for approval; affirmative approval by FDA is not required for continued marketing; and no user fee will apply to such notifications. No other pre-market notification or submission requirements will apply to IVCTs introduced by laboratories prior to enactment. To the extent possible, New York State will provide FDA access to its approval records.
- For IVCTs introduced after enactment but before the delayed effective date of the regulations (*i.e.*, 4 years after enactment), the laboratory will have two options:
    1. It may forego a submission under the new submission process and, instead, submit post-market analytical and clinical validity data after the delayed effective date of the regulations (*i.e.*, 4 years after enactment). The post-market data submission would be subject to a user fee.
    2. After the effective date of the regulations (*i.e.*, 3 years after enactment), but before the delayed effective date of the regulations (*i.e.*, 4 years after enactment), the laboratory may submit the IVCT for approval under the new submission process. No user fee or post-market data submission would apply to the IVCT. New York, and any other CLIA or state submission requirements, would be preempted for that IVCT.
- For IVCTs introduced after the delayed effective date of the regulations (*i.e.*, 4 years after enactment), laboratories must comply with the new submission requirements.

12. Incentives for Innovation

Incentives for IVCT innovation will be included.[40] A priority voucher system will be established for innovative IVCTs (*i.e.*, an IVCT for which there is no existing IVCT with the same intended use and for which the IVCT could lead to a meaningful improvement in treatment or therapy). The voucher will entitle the holder to a reduction in review time. The voucher will be issued upon approval of the innovative IVCT, it will be transferable, and there will not be an additional fee to use or transfer the voucher.

To promote collaboration between the clinical laboratory and manufacturing communities, and the advancements in care that result from such collaboration, two safe harbors from restrictions on off-label promotion will be established for:

- Legitimate scientific communication and collaboration between finished product developers and the clinical laboratories that use those finished products.
- Discussions between a platform manufacturer and a prospective platform purchaser with regard to the manufacturer's test development activities that are relevant to evaluation the platform's capabilities and value.

Improvements to reimbursement and coverage for IVCTs will also be considered.

13. Agency Implementation

Many provisions in this proposal grant discretion to regulatory agencies. As legislative text is drafted, various parameters and limitations on that discretion will be considered.[41] In addition, the following will help to ensure alignment of Agency actions with Congressional intent:

- Rigorous initial and ongoing training will be required for employees of the new FDA center, including specific training on the new standard (*i.e.*, clinical validity and analytical validity) and FDA-regulated activities within a clinical laboratory. The FDA will publish a plan for public comment on the training of FDA employees and contractors on the new statute. The FDA will complete training within one year of finalizing the educational plan.
- All interpretation and implementation will utilize formal (APA) notice and comment rulemaking.
- Executive bonuses at the agency will be tied to performance consistent with the new statutory framework.
- Senior management of the new Center shall include at least one person with management experience in clinical laboratory operations.
- FDA will be required to issue an annual report to Congress on implementation, including an explanation of how implementation has accounted for the unique characteristics of IVCTs and differed from historic regulation of medical devices.

[40] Aside from the specific proposals in this Section, the proposed scheme, as a whole, promotes innovation in other ways. The proposed submission process, for example eliminates undue regulatory burden and improves the time to market.
[41] Particular attention will be given to timeframes.

- Executive-level approval will be required for certain decisions or actions that significantly impact developers.

14. Conclusion

The regulatory framework proposed in this document addresses longstanding concerns with the regulation of diagnostic tests, including issues highlighted in FDA's recent draft guidance on LDTs. The proposal promotes patient welfare, advances innovation, protects patients, provides a predictable and timely path to market, avoids duplicative regulation, and applies the same regulatory principles to the same activity regardless of entity type

ADDENDUM 1: Grandfathering

As outlines in Section 11.1, grandfathered IVCTs will stay on the market unless the following provisions are triggered.

1. Application Option

This provision would not apply to a legally marketed in vitro diagnostic device that was approved, cleared, or marketed pursuant to an exemption from 510(k) notification.

Before taking action under this provision, FDA would conduct a literature review and would create an administrative file. If FDA makes a determination based on all available data and information that:

- The IVCT presents an unreasonable risk of illness or injury when used as intended

  or

- The IVCT is being marketed by its developer with materially deceptive or fraudulent analytical or clinical claims

and notifies the IVCT developer[42] in writing of that determination, the developer may submit an application to market the IVCT without a misbranding finding by FDA.

- Details on timeline for submission, availability of pre-sub type meeting, and classification of IVCT need to be worked out.

- FDA would consider, as part of the submission, previously unpublished data from the developer and the developer's description of the past marketing of the test.

An IVCT subject to this provision shall be deemed to be misbranded if:

- FDA makes the determination described above and the developer does not submit an application within 120 days (or longer, as agreed to by the developer and FDA in a pre-submission conference) of FDA notification, or does not withdraw the test from the market and notify FDA of that fact in writing; or

- The application to market the IVCT is denied.

FDA will offer the developer a pre-submission conference within 30 days of making the above determination. The IVCT shall remain on the market during the pendency of FDA's review of the submission unless FDA triggers the misbranding provision below.

2. Findings of Misbranding

This provision would apply to any IVCT including a grandfathered IVCT. An IVCT shall be deemed to be misbranded whenever the Secretary finds, based on all available data and information, that an IVCT presents an unreasonable and substantial risk of illness or injury when used as intended.

[42] The entity that is responsible for the "reasonable probability of unreasonable risk" or the "materially deceptive or fraudulent" claims would be deemed to be a developer.

3. Practice of Medicine

Nothing in this scheme is intended to infringe upon the practice of medicine.

ADDENDUM 2: Submission Content for Moderate-Risk IVCTs

Documentation Submitted	Description
Submission Coversheet	Includes checklist with items required to be submitted (i.e., items listed in this table of contents).
Cover Letter	Clearly identifies type of submission, name of submitter (including name, address, phone, e-mail address,); name of developer if different from submitter, statement of whether it is an original submission or modification to an existing IVCT.
Intended Use	Includes the developer's intended purpose for the test, including the target being measured or detected, its function (screening, monitoring, predicting, diagnosing, aiding in diagnosis), whether it is qualitative or quantitative, etc.
Developer Information	Developer name, address, and establishment registration number (e.g., lab or company registration number issued by FDA) where IVCT is produced/manufactured.
IVCT Name	Name (brand name or published testname) under which the IVCT will be made available.
IVCT Description Overview	The IVCT Description Overview includes: • Brief description of a scientific basis for the test and explanation of the assay including the target being measured (what does it detect, e.g. enzyme), • Brief description of the principle of the assay method or instrument operation, • classification of the IVCT (if known), • Brief description (list) of components, identification of instrumentation to be used (if applicable),

	• Brief description of software including algorithms, product specifications, • intended use, target populations, users and user environment (e.g., lab, point of care, OTC), • sample/specimen types, • Brief description of method of specimen collection and transport, • • If submitted as part of a closed system, identification of pertinent information.
Performance standards, voluntary standards or mitigations	Identification of performance standards (e.g., CLSI, ISO), voluntary standards or mitigations applicable to the IVCT.
Executive summary of data and information supporting submission	High-level summary of IVCT validation (data establishing analytical and clinical validity.)
Truthful and Accuracy Statement	Declares that the information provided in the submission is truthful and accurate. Signed by the developer and submitter, if different from the developer.
Proposed Labeling	Developer's proposed labeling for the IVCT[43]

[43] Laboratory testing directories or catalogues generally make the following information available to health care professionals regarding tests performed, whether an IVCT protocol or an IVCT finished product is being used to perform patient testing:

- Proprietary name and established name of the test
- Intended use or uses of the test
- Summary and explanation of the test
- Specimen collection and preparation
    - Special precautions including special preparation of the patient
    - Preservatives, etc. to maintain specimen integrity
    - Known interfering substances
    - Recommended specimen storage, handling, shipping, and maintenance
- Results
- Limitations of the procedure
    - Known extrinsic factors or limiting substances
- Expected values
- Specific performance characteristics
    - Accuracy, precision, specificity, and sensitivity

Bibliography

Risk Assessment	Summary describing the methods used in conducting the risk analysis and describes the risks associated with the IVCT and how those risks have been controlled to an acceptable level. (Identify any standards for risk assessment that were followed, e.g., ISO 14971 and other risk management standards)
Software Information	Summary of software necessary for application of the IVCT, including security of data and privacy where applicable.
Summary of IVCT Design Control Activities and Declaration of Conformance to Design Controls	A concise summary of design control activities. Includes a statement that all verification and validation activities were performed and the results demonstrate that the predetermined acceptance criteria have been met.
Evidence to Demonstrate Analytical Validity	Description of peer-reviewed literature and other existing evidence supporting analytical validity, as applicable to the product, as well as summary description of protocols and data from tests demonstrating accuracy; limit of detection, limit of quantification, and/or limit of blank; analytical specificity; precision; linear range; reference intervals; cut-offs; traceability to reference method;; sample stability; interferences, and stress testing, as applicable. Verification and validation of assay procedure and software, as applicable. All provided in a summary format. Summary description will include the following sections; Protocol summary, Pre-Determined Acceptance critiera, Results summary, and Proposed Package Insert Labeling (as applicable). May include usability/human factors testing, depending upon IVCT.
Evidence to Demonstrate Clinical Validity	Description of peer-reviewed literature, and other existing evidence supporting clinical validity, as applicable to the product as well as

	summary description of protocols and data from tests demonstrating clinical validity, including summary of each protocol and criteria used in evaluation or declaration of conformance to recognized standard or mitigation. Protocol and data to be provided in a summary format. Summary description will include the following sections; Protocol summary, Pre-Determined Acceptance criteria, Results summary, and Proposed Package Insert Labeling (as applicable).
Interpretation of Results	

ADDENDUM 3: Modification Submission Triggers

A developer will be required to submit modification information to the FDA in the following instances:

1. A modification has been made to a low-risk IVCT that changes the intended use such that the IVCT is now a moderate- or high-risk IVCT, or
2. A modification has been made to a moderate- or high-risk IVCT that changes the intended use to another moderate- or high-risk use, or
3. A modification to a low-risk IVCT such that the low risk IVCT does not meet required mitigations established for that low-risk IVCT, or
4. The risk assessment of a modification to a moderate- or high-risk IVCT demonstrates that, after consideration of the results of verification and validation studies and relevant mitigations, there is a reasonable probability that there is a meaningful and not remote increase in risk to the patient or user for the intended uses as compared to the risk profile for the IVCT at the time of approval.
    a. No submission is required if the risk assessment of a modification to a moderate- or high-risk IVCT demonstrates for the intended use that there is not a reasonable probability that there is a meaningful increase in patient or user risk or that any such increased risk is remote as compared to the risk profile for the IVCT at the time of approval.
    b. The developer shall submit a notification to FDA at or before the initial commercial use of an IVCT if the risk assessment of the modification to the IVCT prior to consideration of the results of verification and validation studies and mitigations demonstrates that there is a meaningful and not remote increase in risk to the patient or user as compared to the risk profile for the intended uses at the time of approval but the verification or validation studies or mitigations demonstrate that there is not a meaningful increase in such risk for the intended uses or that any such increase in risk is remote.

        Such notification shall include:

        - The identification of the IVCT
        - A short summary of the modification
        - A short summary of the meaningful and not remote risks identified by the risk assessment
        - A short summary of the validation and verification methodologies or the mitigations employed and a short summary of the results of such validation and verifications studies.

        The submission shall be no more than [5] pages.

A modification is made to a moderate- or high-risk IVCT that, following verification and validation using methods and criteria approved or included in the original or subsequent premarket submission, the analytical or clinical performance for the intended uses is

demonstrated to be outside of the approved analytical or clinical performance claims for the intended uses.

5. A modification is made to a moderate- or high-risk IVCT that, following verification and validation using methods and criteria approved in the original or subsequent premarket submission, the analytical or clinical performance for the intended uses is demonstrated to be outside of the approved analytical or clinical performance claims for the intended uses. FDA's decision summary would include sufficient information for a laboratory to appropriately implement any new specifications or mitigations.

If the developer demonstrates and documents that a modification to a moderate- or high-risk IVCT satisfies an FDA recognized standard (e.g., CLSI, ISO) or FDA guidance document applicable to that IVCT modification, no premarket submission is needed. On an annual basis, the developer will submit a summary report such modifications (i.e., modifications per standards) to FDA and shall maintain internal documentation of the modification.

FDA shall have access to documentation relating to the modification, risk assessment, validations or verification studies and mitigations, applicable, during establishment inspections.

Examples: The following modifications may require a submission under the above construct:

- a change in the measurement method (e.g., change from direct to indirect measurement of an analyte)
- a change in the detection method (e.g., change from colorimetric to fluorescent detection, change from polyclonal to monoclonal antibody)
- a change in the interpretation method (e.g., change from visually read results to machine read results)
- a change in measurement output (e.g. qualitative to quantitative)
- Combining reagents from two different approved IVCTs to create a new IVCT
- a change in the analyte(s) measured (e.g., the addition of new inputs/variables to an IVDMIA)
- addition of a new clinical indication (e.g., claim to assess risk for additional disease)
- addition of a new indicated patient population (e.g., addition of claims for neonatal testing to a blood glucose meter cleared only for adult testing)
- a change in test setting (e.g., lab, point-of-care, OTC)
- a change in specimen type (e.g., a change from hair to saliva), unless the validation protocol and acceptance criteria for this type of modification was approved or included as part of the IVCT submission or approval.

Examples of modifications that would not require a submission:

- Specimen stability changes that do not result in changes to analytical or clinical performance outside of the approved range of performance specifications
- Equivalent replacement of a component of the IVCT (e.g., use of a new lot/batch of the same monoclonal or polyclonal antibody, use of a different but equivalent buffer solution, change in vendor for enzyme)

- Reconfiguration that doesn't affect measurement, detection, or interpretation method (e.g., modified outer case for an instrument, lyophilized control material instead of ready to use)
- Addition of new limitation (e.g., new interference)
- Removal of one of multiple indications (e.g., removal of 1 of 2 approved patient populations)
- Selection of one of several cleared indicated patient populations (e.g., specifying a Vitamin D test is for pediatric testing when cleared for all patients)

Grandfathered IVCTs: For purposes of determining whether a change to a grandfathered IVCT requires a submission, the “approved intended use” and the “approved analytical and clinical performance specifications” shall be deemed to be the intended use and labeled claims of the laboratory test protocol as they exist three months before the enactment date of this statute.