

# A PROPOSED REGULATORY FRAMEWORK FOR *IN VITRO* CLINICAL TESTS

Diagnostic Test Working Group

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This document is a progress report on development of a consensus proposal for a new regulatory scheme for *in vitro* clinical tests by the Diagnostic Test Working Group, a coalition of leading diagnostic manufacturers and clinical laboratories. 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 products used in laboratory or other healthcare professional settings, and other tests are products for consumers to use outside of a healthcare facility at home. A laboratory developed test (LDT) is a type of test offered as a service that is intended for clinical use and is designed, developed, and performed within a single laboratory entity. LDTs have sometimes been referred to as “in-house developed” tests.

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 currently regulates the safety and effectiveness of diagnostic test products as medical devices, including the design, manufacturing, and post-market monitoring of such tests. 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.<sup>1</sup>

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).

FDA recently issued draft guidance documents on its proposed regulation of LDTs.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. FDA has asserted that such regulation is necessary to ensure that such tests are safe and effective. FDA asserts that it may now regulate LDTs because the circumstances surrounding the conduct of LDTs and the tests themselves have changed since FDA initially decided to exercise its enforcement discretion over such tests.

Whether, and to what extent, LDTs should be regulated by the FDA has been a subject of great debate. Many clinical laboratories maintain that LDTs should not be regulated by FDA because: (1) LDTs are fundamentally different from medical devices; (2) LDTs do not meet the statutory

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<sup>1</sup> 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.

definition of a “medical device” under 21 U.S.C. § 321(h); (3) FDA has not followed legally required processes to regulate LDTs; (4) FDA does not understand the laboratory environment; (5) the laboratory environment and utilization of LDTs is vastly different than the manufacturing environment of other diagnostic tests; (6) LDTs already undergo regulatory review through CLIA and often through third party accreditation or state statutory regulations; (7) FDA lacks the resources necessary to regulate LDTs in addition to its current workload; and (8) FDA regulation of LDTs as medical devices would be harmful to public health by interfering with the practice of medicine and eliminating or delaying access to innovative tests needed for patient care.

Others, however, express concern that LDTs, such as certain genetic tests for disease risk, may be marketed to consumers without adequate oversight or assurance of clinical validity. Certain stakeholders also contend that the current state of affairs unfairly benefits LDTs because FDA is not regulating the same activities or same diagnostic tests in the same manner.

Determining which federal agency should have regulatory oversight of *in vitro* diagnostic tests is an important issue to both manufacturers and laboratory companies. Many such companies have expressed the imperative need to have clear and logical lines separating the development of diagnostic tests from the actual conduct of a diagnostic test.

Furthermore, the practice of medicine involved in consultations about, and the interpretation of, the test performance or 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 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, excessive 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 advancement 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 and reimbursement 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. Advance fair and prompt reimbursement.
11. Maintain the practice of medicine.
12. 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,<sup>2</sup> in making treatment or health-based decisions. While “safety and effectiveness” is 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 often used 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.

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<sup>2</sup> 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.

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,<sup>3</sup> 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, that blood screening tests regulated under Section 351 of the Public Health Service Act are not *in vitro* clinical tests.

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.

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.<sup>4</sup> 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.<sup>5</sup> A component or raw material is not a finished product, nor a drug, device, or biological product.<sup>6</sup>

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.

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<sup>3</sup> This is intended to capture software, to the extent otherwise regulated.

<sup>4</sup> This is distinct from the laboratory's standard operating procedure (SOP), which describes the process or service of actually performing the test.

<sup>5</sup> 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.

<sup>6</sup> Supplier controls adequately protect patients. This structure is similar to the current regulatory approach for HCT/P blood products.

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.<sup>7</sup>

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

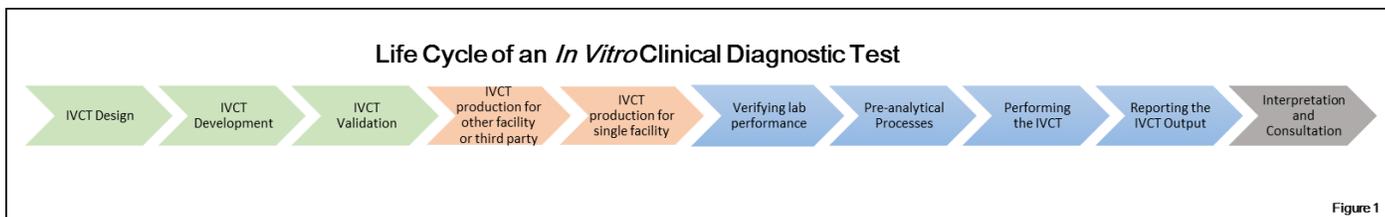
*A platform is an article comprised of hardware and, in many cases, software that is designed and intended by the developer to perform multiple different in vitro clinical tests.*

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), 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.



The 10 steps in the IVCT life cycle are:<sup>8</sup>

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.

<sup>7</sup> The new definition increases regulatory focus and efficiency by concentrating on finished products and laboratory test protocols rather than raw materials or components.

<sup>8</sup> 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.

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.
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.<sup>9</sup>

### 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. Regulatory requirements cannot be allowed to unnecessarily slow and restrict access to new and innovative IVCTs. 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.

## 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:

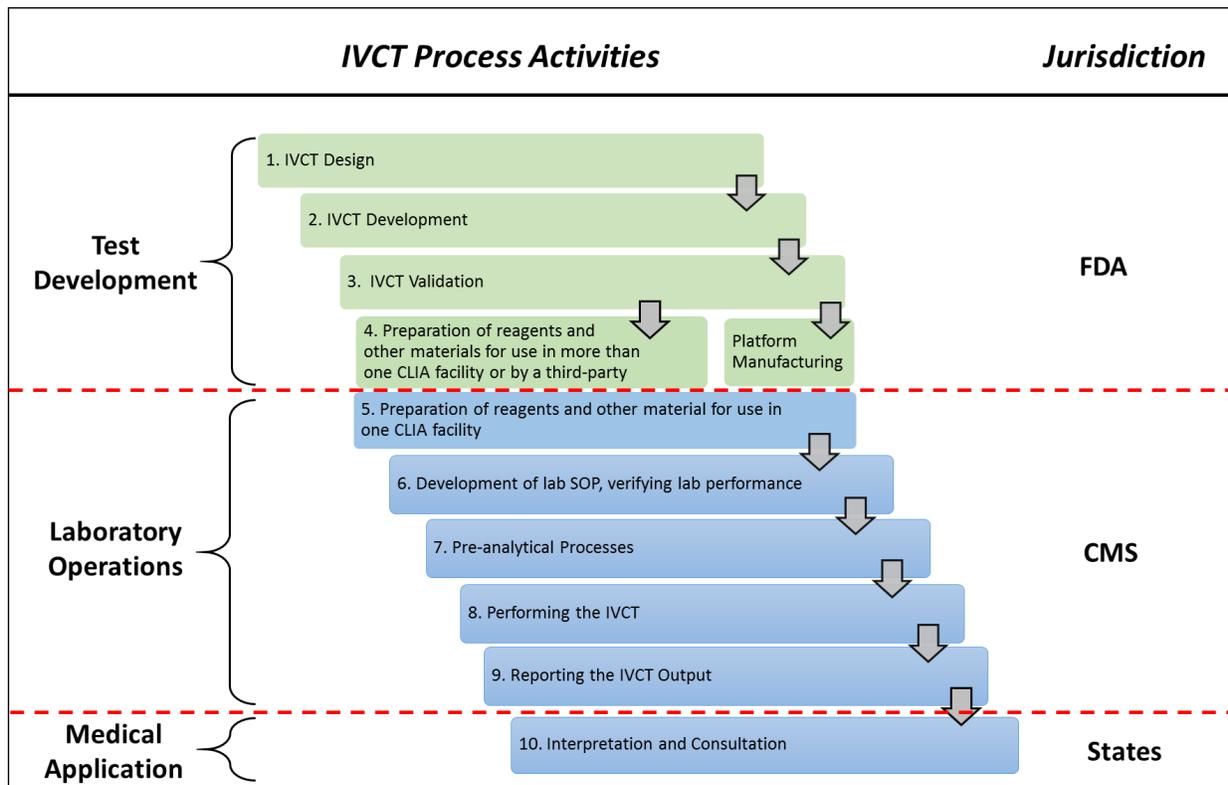
- The process of developing an IVCT (*i.e.*, design, development, and validation) is uniquely different from the process of performing an IVCT (*i.e.*, actually testing a specimen) that has already been developed.
- Existing regulatory authorities have important existing competencies with regard to development 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

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<sup>9</sup> 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.

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.<sup>10</sup>

## 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.<sup>11</sup>

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.<sup>12</sup> 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.

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<sup>10</sup> 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.

<sup>11</sup> 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.

<sup>12</sup> 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.

For this purpose, a *facility* means a single establishment with a unique CLIA certificate.<sup>13</sup>

### **4.3. CMS Jurisdiction Over Lab Operations**

CMS has extensive institutional knowledge and capacity with regard to laboratory operations.<sup>14</sup> 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.<sup>15</sup>

### **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.

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<sup>13</sup> 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.

<sup>14</sup> 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.

<sup>15</sup> 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. 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.

### 5.1. Risk Classifications

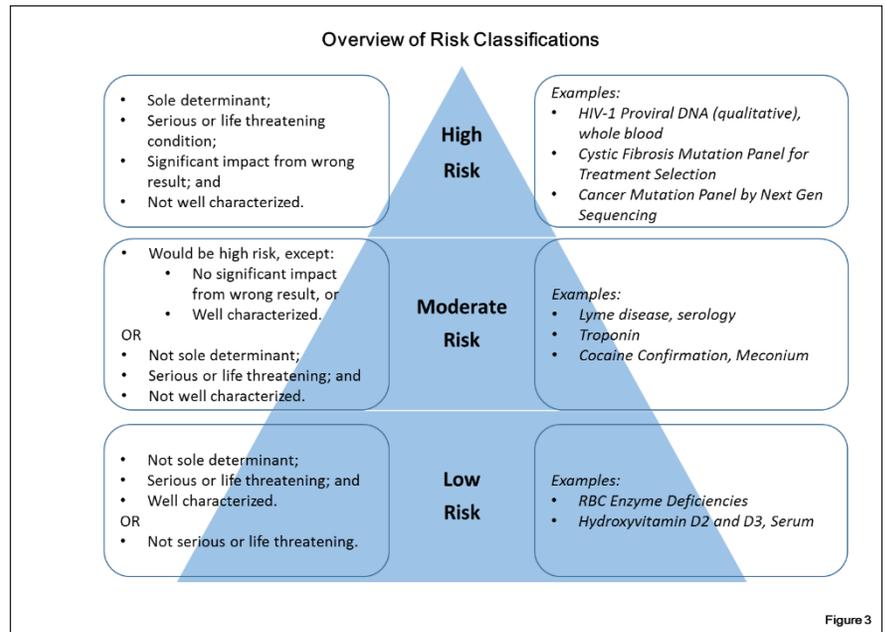
All IVCTs will be classified as high-risk, moderate-risk, or low-risk tests. The premarket, quality, and post-market requirements will vary by risk class.

<b>RISK CLASSIFICATIONS</b>
<p><b>High Risk:</b> 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.</p>
<p><b>Moderate risk:</b> 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.</p>
<p><b>Low Risk:</b> An IVCT that is not a high-risk IVCT or moderate-risk IVCT.</p>

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.<sup>16</sup>



A *permanent impairment* is an irreversible impairment or damage to a body structure or function, excluding trivial impairment or damage.<sup>17</sup>

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.

<sup>16</sup> This definition draws upon the definition of “serious injury” in 21 C.F.R. § 803.3.

<sup>17</sup> 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. 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 and a proposed test description. The FDA must reject or agree to the proposed classification within 60 calendar days. If the FDA does not affirmatively reject or agree to the proposed classification within 60 calendar days, the proposed classification will be considered approved and must be published by the FDA.

Rejection of a proposed classification will trigger appeal rights. An appeal can include a request for review by an advisory panel.<sup>18</sup>

Prior to submitting a request for classification, the developer may request an informal discussion with the FDA, similar to a pre-submission conference.

### **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.
- 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.

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<sup>18</sup> Time frames for hearing an appeal will vary depending on whether a panel is used. An appeal does not preclude a reclassification request.

### 5.1.3. 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.

A classification advisory panel with balanced stakeholder representation, including physicians, consumers, members of the diagnostic industry and laboratory community, will use a public process to develop and issue classification recommendations on all currently classified and non-classified IVCTs. The advisory panel will issue recommendations for all currently classified Class II and Class III IVCTs within one year after enactment, and it will issue recommendations for all currently exempt IVCTs within one year after the deadline for listing IVCTs described in section 11, below. The advisory panel's recommendations will be subject to a 90 day notice-and-comment period.

Within six months of receiving the advisory panel's recommendations, the FDA may accept or revise the advisory panel's recommended classification for a particular IVCT. This six-month period is non-extendable. Any revisions made by the FDA must take into consideration comments filed during the notice-and-comment period and must be accompanied by a written explanation that describes the scientific and clinical basis for the revision. All classification recommendations issued by the advisory panel that are not revised by the FDA within six months will be classified in accordance with the advisory panel's recommendations. After that time, all classifications and reclassifications must follow the process described above in sections 5.1.1 and 5.1.2.

Any classification decision made pursuant to this section can be immediately appealed. Standard FDA administrative procedures for the appeal of agency actions will apply.

## 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.<sup>19</sup>

**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;<sup>20</sup>
- Clinical guidelines;
- Expert opinion;
- Bench studies, including use of archived specimens;
- Past experience with similar products;
- Case studies;
- Clinical data;
- Consensus standards;

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<sup>19</sup> Although clinical utility may be relevant for reimbursement purposes, it is not a criterion for marketing an IVCT.

<sup>20</sup> The underlying data is not required.

- 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 be signed by the chief scientific officer or other member of senior management at the FDA center.

### 5.2.2. 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.<sup>21</sup> 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 data that establishes analytical validity and information to support the reasonable belief of clinical validity (*i.e.*, a summary clinical evidence report).

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.

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<sup>21</sup> The declaration of conformity to quality requirements, and the Agency's authority to inspect, are sufficient to ensure manufacturing quality.

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
- 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<sup>22</sup> 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.<sup>23</sup>

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 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;<sup>24</sup> or

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<sup>22</sup> This refers to an entity that controls, is controlled by, or is under common control with, the developer of the laboratory test protocol.

<sup>23</sup> 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.

<sup>24</sup> 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

- 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.

**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 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.<sup>25</sup>

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

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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.

<sup>25</sup> 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.

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 electronic copy of the label.<sup>26</sup> 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:

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<sup>26</sup> 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

- 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**

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.

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.

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 15 calendar days<sup>27</sup> for any adverse event known to the developer that involves actual patient death or 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;
- 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.<sup>28</sup> 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.

Such 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 with knowledge of an adverse event may also report.

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<sup>27</sup> The present obligation to report within five days is too short to allow a proper investigation of the situation and preparation of a report. A longer timeframe will enhance the accuracy of the information reported.

<sup>28</sup> Similar trend-based reporting is utilized in the pharmaceutical industry. These reports will be based on investigated events.

### **5.6.2. Correction or Removal Actions**

Developers should voluntarily conduct correction or removal actions for an IVCT. FDA may mandate a correction or removal action if the developer refuses to conduct such action voluntarily and such action is necessary to prevent, eliminate, or reduce a serious risk to patient health. Procedures, records, and reports for correction or removal actions will generally follow 21 C.F.R. Part 7 and 21 C.F.R. § 806, subject to the following changes:<sup>29</sup>

- FDA will classify correction or removal actions within seven days of receiving notification.<sup>30</sup>
- Notifications or information received by developers that are related to laboratory operations are not considered correction or removal actions (*i.e.*, only IVCT errors are even potentially reportable).
- A corrected or updated patient-specific laboratory report is not a correction or removal action.
- Enhancements are not corrections.<sup>31</sup>

### **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.

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<sup>29</sup> See also section 10 on enforcement.

<sup>30</sup> The current FDA process for classifying corrections and removals, and the delays in such classifications creates significant confusion in the marketplace. When classification follows the actual correction or removal, the press release accompanying the classification routinely causes health care provider and other stakeholders to question whether the press release is announcing a new, separate correction or removal.

<sup>31</sup> A "hold" on a test during investigation is not a removal action.

## 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.<sup>32</sup>

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 validity. Each individual IVCT performed using a platform is separately regulated based upon the individual IVCT’s characteristics.

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

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<sup>32</sup> 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.

## 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.

## 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.<sup>33</sup> 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.

## 7.4. Rare Disease

A *rare disease IVCT* is an IVCT, other than an emergency use IVCT, that is intended to identify, measure, predict, monitor, or assist in selecting treatment for, a rare disease (*i.e.*, a disease with

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<sup>33</sup> 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 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.

which fewer than 200,000 people in the United States have been diagnosed as having the disease at the time of notification).

Rare disease IVCTs are subject to special premarket requirements. The developer of a rare disease 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 a rare disease 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 a rare disease 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 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.

## **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<sup>34</sup>; 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<sup>35</sup>; and
- 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.

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<sup>34</sup> "Requirements in effect" or other approaches will be considered to avoid gaps during transition.

<sup>35</sup> Licensure requirements cannot include conditions of licensure that are different than CLIA.

## **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 apply at the 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 will utilize existing systems and processes for inspections, enforcement, and penalties, except provisions for inspections by accredited third-parties will be developed. There will be no duplicative inspections.

CMS will utilize existing systems and processes for inspections, enforcement, and penalties.

### **10.2. Recalls 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**

### **11.1. 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.

### **11.2. 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.

### **11.3. Test Development Activities**

#### **11.3.1. 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.

### **11.3.2. 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.

### **11.3.3. 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.

#### **11.3.4. 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.<sup>36</sup>

#### **11.3.5. 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

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<sup>36</sup> 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.

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.<sup>37</sup> 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.

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<sup>37</sup> 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.

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.<sup>38</sup> 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.
- 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.
- FDA will be required to issue annual reports on implementation, including an explanation of how implementation has accounted for the unique characteristics of IVCTs and differed from historic regulation of medical devices.
- 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.

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<sup>38</sup> Particular attention will be given to timeframes.