EXECUTIVE SUMMARY

Diagnostic Test Working Group Proposed Regulatory Framework For *In Vitro* Clinical Tests

March 5, 2015

The Diagnostic Test Working Group, comprised of diagnostic industry and clinical laboratory participants, has developed this draft proposed regulatory framework to address longstanding concerns with the regulation of diagnostic tests, including issues highlighted in FDA's recent draft guidance on LDTs. The draft proposal advances innovation for patient benefit, protects patients, provides a predictable and timely path to market, ensures reasonable risk-based regulation, avoids duplicative regulation, advances precision medicine, and applies the same regulatory principles to the same activity regardless of entity type.

Each Coalition member must obtain final senior executive approval of the final, complete proposal.

Scope, Structure, and Jurisdiction

The proposal would apply to any *in vitro* clinical test (IVCT), which includes both finished products (*e.g.*, test kits and platforms) and laboratory test protocols. IVCTs would be a new category under the FD&C Act. IVCTs will not be regulated as devices, drugs, or biologics.

The existing regulatory structure, under which regulatory requirements are tied to the type of entity (*i.e.*, a manufacturer or a laboratory), will be replaced by a construct under which the type and level of regulation is based on the activity being performed, regardless of the type of entity performing that activity. All entities performing the same activities will be regulated equally. For example, the same requirements will apply to a laboratory when developing an IVCT (*i.e.*, a finished test or protocol) for distribution to another facility as apply to a manufacturer that develops an IVCT for distribution.

The ten activities in the process of developing, producing, performing, and using the results of an IVCT are shown in Attachment A. There will be three distinct, non-overlapping categories of activity:

- **Test development,** which includes the design, development, and validation of an IVCT as well as the production of an IVCT for distribution to another facility or third-party.
- **Laboratory operations**, which are all of the activities necessary to actually perform or "run" a developed IVCT, including the preparation of reagents for use in a single CLIA facility, sample preparation, and other pre-analytical processes.
- **Medical Application,** which includes the interpretation of an IVCT output by a health care professional and the related medical consultation.

A new FDA center will have sole and exclusive jurisdiction over all test development activities. CMS, through a revised and modernized CLIA, will have sole and exclusive jurisdiction over all laboratory operations. Jurisdiction over medical application will be reserved to the states.

FDA Regulation of Test Development

The current classification and PMA/510(k) systems for IVCTs will be replaced with a risk-based system that accounts for the distinct characteristics of an IVCT. Each test will be classified as high-risk, moderate-risk, or low-risk. The criteria for, and examples of, risk classification are described in Attachment B. An advisory panel that includes physicians, consumers, industry and laboratory representation will be used to transition existing IVCTs to the new risk classes. The advisory panel's recommended classifications will go into effect unless the Agency affirmatively objects, taking into consideration public comments, within six months of the panel's recommendations.

Developers will propose to FDA the appropriate classification of *new* IVCTs. FDA will have 60 days to object to the developer's proposed classification. If FDA does not act, the proposed classification becomes effective. A reclassification process may be initiated by any person (including FDA) and will use an advisory panel if requested.

To market an IVCT, the developer must establish a reasonable assurance of analytical validity and clinical validity for the intended use. This new premarket standard is better aligned with diagnostics. The therapeutic device standards of "safe" and "effective" are not applicable to IVCTs—analytical and clinical validity are the appropriate measures. Premarket submission/listing requirements will be as follows:

Classification	Premarket Requirement
High-Risk	• Submit for affirmative approval prior to commercialization; FDA decision within 90 days • Evidence must establish analytical and clinical validity • No premarket inspection or detailed manufacturing information • Declaration of conformity to quality requirements must be submitted
Moderate-Risk	• Submit prior to commercialization • Within 60 days, FDA may object or request post-market reports on clinical validity; absent objection, the IVCT is automatically approved • Submission must establish analytical validity and a reasonable belief of clinical validity
Low-Risk	• Notify FDA of IVCT name and intended use within 10 days after commercialization

Special pathways will be available for IVCTs for rare diseases, emergency use, and unmet needs. User fees will be required, but will not be the primary funding source for the new regulatory structure (*i.e.*, approximate the current device funding ratio of 20–25%). CLIA fees will be credited against FDA fees.

Submission of a modification (by the developer or by a laboratory that purchases a finished test) will only be required if the modification:

- Has a meaningful clinical impact, post-verification and –validation, or
- Changes the intended use of the IVCT (to a high- or moderate-risk use).

Quality requirements for test development activities will include:

- Finished products and laboratory developed protocols will be subject to design controls.
- Production of finished products for distribution to other facilities and third parties will be subject to updated FDA quality requirements.
- Component and raw material suppliers will be subject to supplier controls rather than direct FDA oversight.
- Modernized CLIA obligations, not FDA quality system requirements, will apply to laboratory operations, but will be harmonized with FDA requirements as appropriate.

Post-market systems and obligations will largely resemble current FDA requirements, except adverse event reporting will be updated to: (1) limit submissions to those that have a serious impact on health, and (2) leverage summary and trend reporting where public health does not benefit from event-specific reporting. There will be no overlap of CLIA and FDA requirements.

CMS/CLIA Regulation of Laboratory Operations

CLIA, exclusively, will regulate laboratory operations. CLIA will be revised to:

- Modernize applicable requirements to standards comparable to those under the College of American Pathologists (CAP) certification program.
- Harmonize quality requirements with FDA requirements where appropriate (*e.g.*, purchasing controls).
- Eliminate requirements related to test development, which will now be regulated by FDA.

Other Key Provisions

Federal regulatory agencies will have the authority to withdraw from the market IVCTs which have been determined to cause serious or life threatening harm when used as intended.

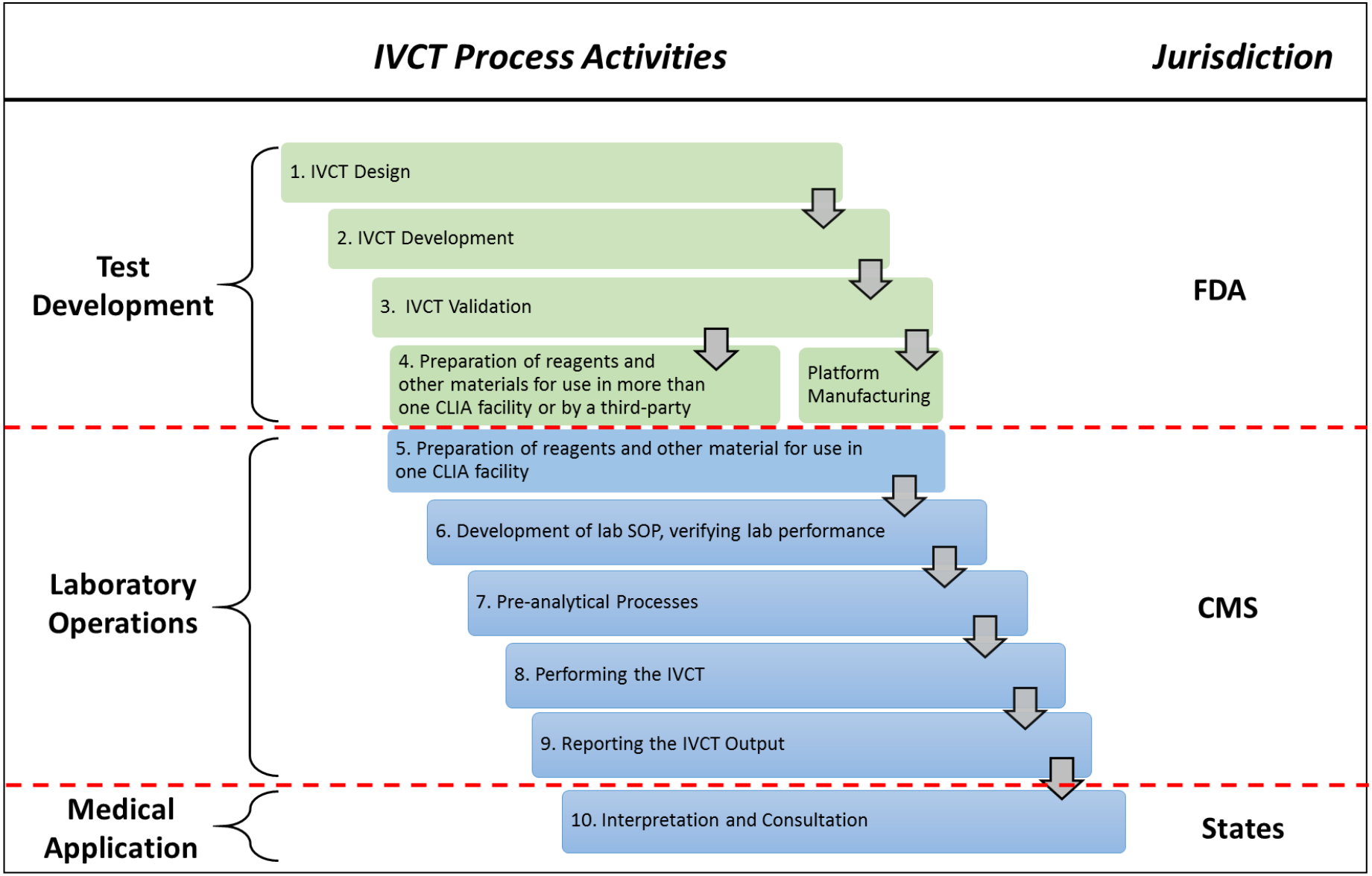
All State requirements different from, or in addition to, FDA or CLIA IVCT requirements will be preempted. CMS may delegate inspection and certification activities to the States.

Incentives for innovation will be established (*e.g.*, priority review vouchers and protections for laboratory-manufacturer collaborations). Several provisions will also help ensure alignment of Agency culture with Congressional intent (*e.g.*, extensive training and oversight reports).

FDA and CMS must promulgate final implementing regulations within two years after enactment. Those regulations will be effective two years after finalization, except the new submission process will be available one year after finalization.

Manufacturers will use existing FDA approval systems for IVCTs developed during the three-year period following enactment, and will begin using the new submission process after three years. For tests developed by clinical laboratories during the four-year period following enactment, laboratories will have the option of (i) submitting post-market data to establish clinical validity after such four-year period, subject to a user fee, or (ii) using the new submission process for approval without incurring a user fee. For IVCTs introduced by laboratories 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 would be required for high-risk ICVTs 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.

Attachment A



Attachment B