The Verifying Accurate Leading-Edge IVCT Development (VALID) Act

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Vital Insights | Transforming Care

Introduction of the VALID Act

March 5, 2020 The “Verifying Accurate Leading-Edge IVCT Development Act” (or “VALID” Act) was introduced in the Senate and House.

Context

Introduction of The VALID Act marks the first time a bipartisan, bicameral bill aimed at comprehensive diagnostics regulatory reform has been introduced.

Formal bill provides all stakeholders opportunity to more fully engage in reform efforts. *However, certain provisions described in this presentation are unclear and require further clarification from the bill sponsors.*

Marks a milestone in AdvaMedDx efforts to secure a diagnostic-specific, risk-based and modernized for innovation, regulation of all diagnostic tests - LDTs and IVDs.

Legislative process will allow AdvaMedDx to pursue member-driven modifications and improvements to the bill.

AdvaMedDx Position on Diagnostics Regulatory Reform

AdvaMedDx supports the establishment, through legislation, of a modernized and predictable, risk-based diagnostics regulatory framework under FDA to which all LDTs and IVDs would be subject.

The framework should recognize the unique characteristics of diagnostic tests, allowing developers to leverage predictable and modernized review pathways, speeding high-quality, reliable and innovative tests to providers and patients, while providing FDA with the tools to administer effective oversight of these tests.

Key Definitions

In Vitro Clinical Test (IVCT)	Includes both laboratory developed tests (LDTs) and traditional in vitro diagnostics (IVDs).
	Specifically included as IVCTs: tests, test protocols, test platforms, articles for taking or deriving specimens from the human body, and software (except software excluded from the definition of a medical device) that are intended to be used in the collection, preparation, analysis, or in vitro clinical examination of specimens taken or derived from the human body for the purpose of: identifying, diagnosing, screening, measuring, detecting, predicting, prognosing, analyzing, or monitoring a disease or condition; or selecting, monitoring, or informing therapy or treatment for a disease or condition.
	The definition of IVCT does not include: certain IVCT components, including blood, blood components, or human cells or tissues; certain articles use for invasive sampling; laboratory equipment; and personal protective equipment.

Key Definitions

Analytical Validity: An IVCT's ability to identify, measure, calculate, or analyze the test's targets, or assist in such efforts. For articles for taking or deriving human specimens, analytical validity means that it performs as intended and will support the analytical validity of an IVCT with which it is used.

Clinical Validity: An IVCT's ability to achieve its intended use, as set forth in the definition of IVCT.

Key Definitions

High-Risk: IVCTs for which undetected inaccurate results would present potential unreasonable risk for serious or irreversible harm or death to patients, or serious harm to the public health; or is potentially likely to result in the absence, delay, or discontinuation of life-supporting or -sustaining treatment. Excluded from the definition of high-risk IVCTs are those for which mitigating measures are sufficient to mitigate these risks.

Low-Risk: IVCTs for which undetected inaccurate results would cause minimal, no, or non-life threatening (or immediately or medically reversible) harm or disability, or only a remote risk of adverse patient or public health impact. Low-risk IVCTs include those for which mitigating measures are sufficient to ensure that they are low-risk.

Mitigating Measures: requirements determined by FDA to be necessary for an IVCT or category of IVCTs to meet their applicable standard (generally, to provide a reasonable assurance of analytical and clinical validity) or to mitigate risk of harm from an inaccurate result or misinterpretation of results. These may cover labeling, advertising performance standards, performance testing, clinical studies, submission of clinical data, user comprehension studies, postmarket studies, training, and conformance to standards.

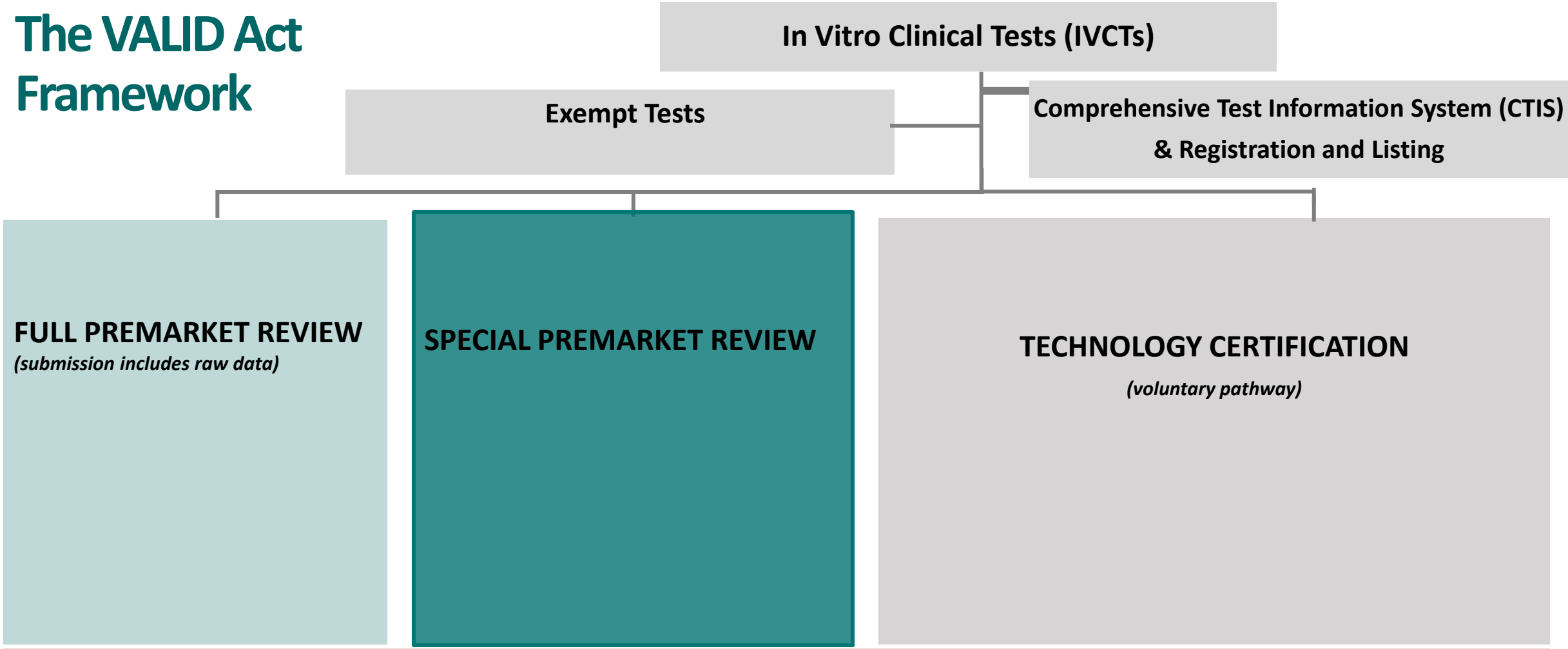
Key Definitions

Applicable Standard: is defined as a reasonable assurance of analytical and clinical validity for most IVCTs. For test instruments, it means a reasonable assurance of only analytical validity. For articles for taking/deriving specimens, it means analytical validity, as well as safety, where applicable.

First of a Kind: is defined as an IVCT with both a different intended use and indications for use than any legally marketed IVCT.

Technology: is defined as a developer's grouping of IVCTs that do not significantly differ in control mechanisms, energy sources, or operating principals and for which design, development, and manufacturing, including analytical and clinical validation as applicable, of the tests would be addressed similarly. The definition also provides examples of technologies, such as immunoassay, mass spectrometry, and next generation sequencing.

The VALID Act Framework



BREAKTHROUGH – An enhancement to Premarket, Special or Tech Cert for eligible tests.

CHANGE PROTOCOLS – All Pathways include Change Protocols for Postmarket Modifications. (Covered changes do not need to be reviewed by FDA.)

The VALID Act Framework

In Vitro Clinical Tests (IVCTs)

Comprehensive Test Information System (CTIS) & Registration and Listing

CTIS

- Public, searchable database of all IVCTs. CTIS would also serve as an electronic submission portal for premarket and Postmarket submissions.
- FDA is directed to create and maintain a CTIS to provide information about IVCTs available on the market, making certain information available to providers and consumers.
- CTIS will include: regulatory pathway designation, registration and listing information, reports of corrections and removals (recalls), and other information.
- CTIS will serve as a portal for submission of premarket applications and technology certification applications, registration and listing information, and adverse event reports.

Registration and Listing

- Registration and listing requirements (collectively, notification) are broader than current device listing requirements.
- Requires registration of establishments by developers, contract manufacturers, contract sterilizers, repackagers, relabelers, and distributors of IVCTs. (Registration subjects the establishment to inspection.)

The VALID Act Framework

In Vitro Clinical Tests (IVCTs)

Exempt Tests

- Certain components and parts
- Grandfathered tests
- 510(k)-exempt tests
- Low-risk tests
- Manual tests
- Humanitarian use tests
- Custom and low-volume tests
- Tests used solely for public health surveillance
- Tests used solely for forensic, law enforcement, or employment purposes
- Technology Certification IVCTs
- Investigational use tests

The VALID Act Framework

In Vitro Clinical Tests (IVCTs)

Exempt Tests

Comprehensive Test Information System (CTIS) & Registration and Listing

FULL PREMARKET REVIEW

(submission includes raw data)

- High Risk
- Cross Referenced (*without mitigating measures**)
- Certain First of a Kind
- Direct to Consumer
- Home Use

SPECIAL PREMARKET REVIEW

- Instruments
- Specimen Receptacles
- IVCTs eligible for Tech Cert
- Cross Referenced (*with mitigating measures**)
- Certain First of a Kind

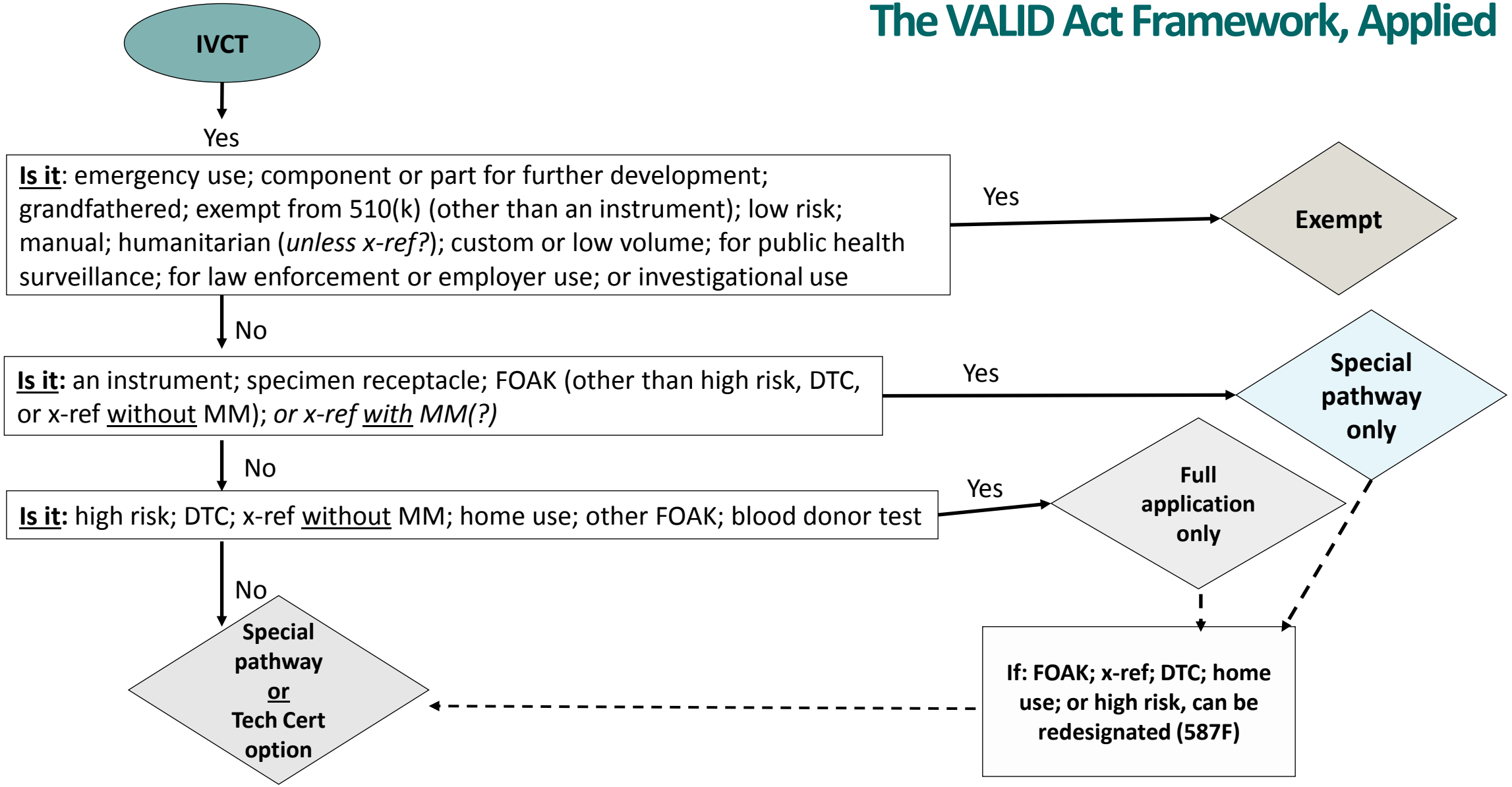
TECHNOLOGY CERTIFICATION

- FDA intends for majority of IVCTs to go through Tech Cert.
- Voluntary pathway can be accessed for eligible test types as an alternative to the default approval pathways.
- Technology Certification would allow FDA to authorize suites of IVCTs utilizing the same technology through analysis of a representative assay and evaluation of the developer's methods and practices.
- While the bill expands the scope of this program so that it can authorize various IVCTs within a single technology, certain test types remain statutorily excluded from eligibility.

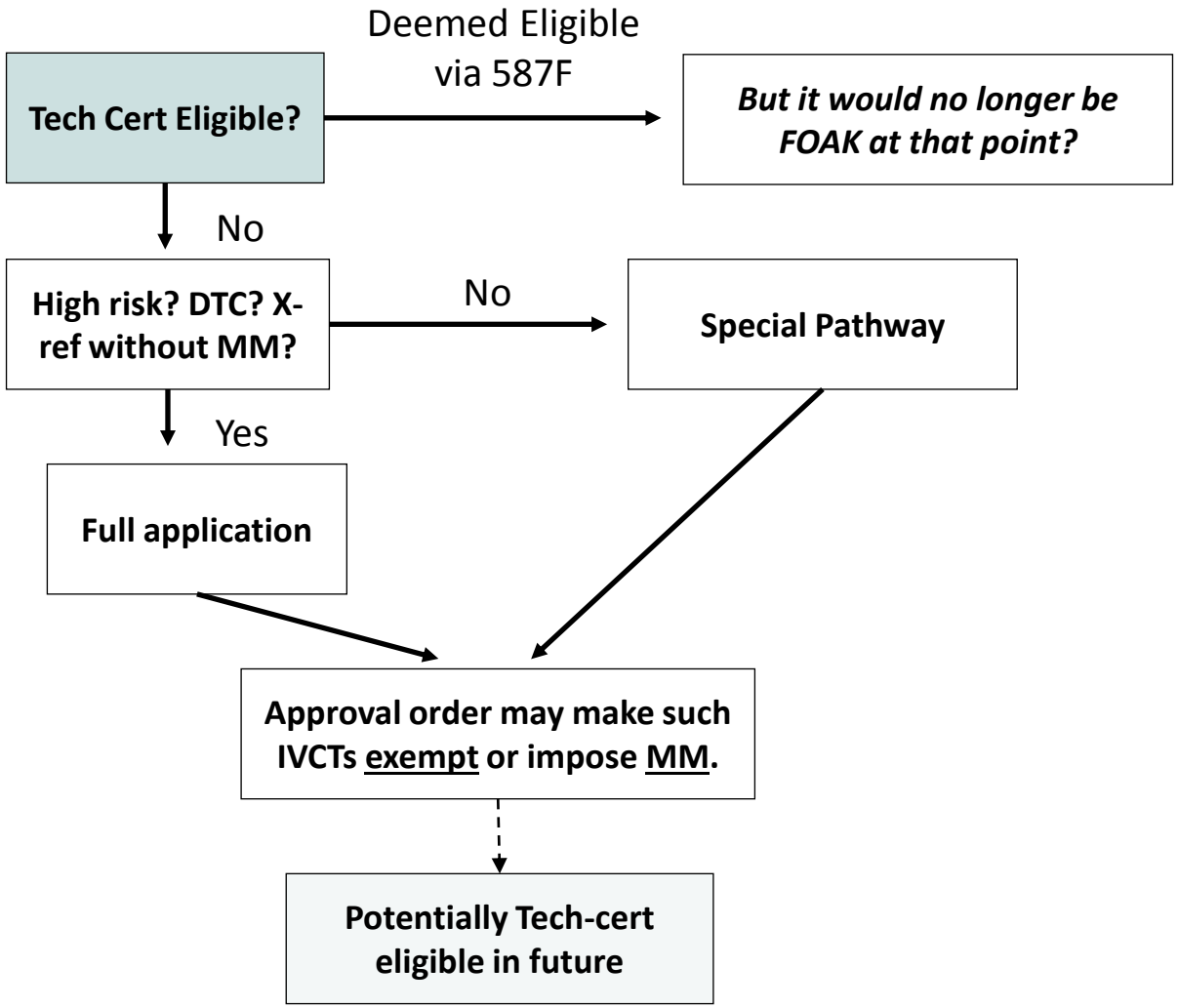
BREAKTHROUGH

CHANGE PROTOCOLS

The VALID Act Framework, Applied



VALID, Applied to First of a Kind (FOAK) IVCTs



Status of Cross-Referenced IVCTs in VALID

Theory of Interpretation (dictating potential clarifying edits):

Special Pathway is open to a FOAK test "unless it is a … cross-referenced test that does not have" MM. (p. 59)

→ ***A cross-referenced test WITH MM IS eligible for the special pathway***

A cross-referenced test is NOT Tech Cert eligible unless redesignated under 587F. (p. 84)

FDA to issue guidance establishing MM for cross-referenced tests (p. 105)

Tech Cert-eligible tests are eligible for the Special Pathway (p. 59)

→ ***Cross-referenced tests with MM will be Tech Cert eligible***

The VALID Act Framework - Review Timelines

FULL PREMARKET REVIEW

Aggregate Review Time 150 Days

- Within 60 days of submission: FDA must file or issue a "Refuse to File" of the submission.
- Within 75 days of submission: FDA must complete a substantive review and issue a statement of deficiencies (if any)
- Within 90 days of "acceptance" (presumably refers to filing): FDA must issue a decision. But can be extended if there is a major amendment.

SPECIAL PREMARKET REVIEW

Aggregate Review Time 120 Days

- Within 60 days of submission: FDA must file or issue a "Refuse to File" of the submission.
- Within 75 days of submission: FDA must complete a substantive review and issue a statement of deficiencies (if any).
- Within 60 days of "acceptance" (presumably refers to filing): FDA must issue a decision. But can be extended if there is a major amendment.

TECHNOLOGY CERTIFICATION

Aggregate Review Time

- Within 90 days of submission: FDA must issue a statement of deficiencies (if any).
- Within 90 days of submission: FDA must issue a decision. Timeline may be extended "by mutual agreement."
- Initial Tech Cert can be up to 4 years; Unlimited number of subsequent Tech Certs for up to 4 years each.

BREAKTHROUGH

- **Breakthrough designation request must be decided upon within 60 days.** (Note: this is the decision whether to grant breakthrough, not the ultimate decision on the application).

VALID Treatment of CLIA

Section 587A: Applicability	Provision specific to laboratories and blood and tissue establishments provides that the framework will not change or modify the Clinical Laboratory Improvement Amendments (CLIA) program or regulatory authority applicable to blood and tissue facilities regulated under sections 351 and 361 of the Public Health Service Act.
	Provides conditions for emergency use, which would allow CLIA labs, in the event of a public health emergency, to use a test pending submission of an emergency use authorization, if certain other conditions are met (validation, notification, and labeling).
Section 587I: Registration and Listing	Required elements include CLIA certificate number

VALID Treatment of CLIA, cont.

Section 587J: Test Design and Quality Requirements	Quality requirements implemented and enforced by FDA only apply to the design and manufacturing of IVCTs, laboratory operations will continue to be regulated by the Centers for Medicare and Medicaid Services (CMS) under CLIA
	Establishes different quality requirements for labs that are and are not CLIA-certified for high-complexity testing
	Directs FDA consider whether the developer participates in an audit program in which the US participates or recognizes, or confirms to standards recognized by FDA. FDA to ensure a least burdensome approach by leveraging appropriate quality assurance requirements applicable to CLIA-certified labs.
Section 6: Emergency Use Authorization (amending Section 564 of the FDCA) & Section 587A (*as added*)	Generally permits IVCTs to be developed and used under an emergency use authorization (EUA).
	This provision would track FDA's recent guidance allowing CLIA labs, in the event of a public health emergency, to use a test pending submission of an EUA

Quality Requirements, Recognized Standards, and Labeling

Quality Requirements	VALID establishes quality requirements applicable to IVCTs in lieu of Quality Systems requirements applicable to devices.
	All registered persons are required to maintain quality requirements tailored to type of IVCT and where it was developed.
	Quality requirements apply to design and manufacturing of the IVCT.
Recognized Standards	FDA can establish performance standards that IVCTs can use to demonstrate clinical validity, analytical validity, and safety (as applicable).
	To establish standards, FDA may rely on standard setting organizations to utilize all or part of appropriate recognized standards, including international standards.
Labeling	VALID establishes requirements for IVCT labeling.
	Includes some exemptions and alternative requirements for certain tests and uses.
	Labeling information should be made publicly available (except for trade secrets/CCI)
	FDA may issue guidance on labeling requirements.

Adverse Event Reporting

IVCT developers are required to establish and maintain an adverse event reporting system, unless exempt.

"Adverse event" is defined to include malfunction reporting.

Time frames for individual AE reports:

- 5 calendar days to report after developer receives or otherwise becomes aware of information that reasonably suggests the adverse event involves a patient death or the event presents an imminent threat to public health.
- Quarterly reports for all other adverse events

Adulteration/Misbranding and Postmarket Remedies

Adulteration and Misbranding	Adulteration criteria specific to IVCTs include failure to conform to mitigating measures, failure to meet conditions of exemptions for clinical use, and failure to meet the quality requirements established by VALID.
	Misbranding criteria specific to IVCTs include failure to comply with VALID's labeling requirements, failure to label in accordance with an applicable mitigating measure, and violating certain labeling and sale requirements for restricted IVCTs.
Remedies	Reports of corrections and removals; postmarket surveillance; other postmarket remedies similar to those for devices.

Collaborative Communities

FDA may participate in “collaborative communities” composed of a diverse set of stakeholders, to facilitate “community solutions and decision-making” regarding IVCTs.

Collaborative communities should have broad representation, including interested private and public-sector stakeholders.

VALID outlines topics that may be part of recommendations by collaborative communities, including mitigating measures, standards, evidence requirements, new technologies, and policy/procedure development for IVCTs.

FDA will issue guidance on collaborative communities within 6 months of VALID’s enactment.

Other Provisions and Features

Authority for accredited persons for application reviews (including technology certifications) and inspections.

Appeals: “significant decisions” require substantive summary of rationale

Preemption provision specific to this subchapter (IVCTs)

Resources: User fee program to be negotiated using process analogous to MDUFA process.

Transition Process

Deeming of current IVDs:

- Cleared and approved IVD devices will be deemed approved IVCTs
- Exempt IVD devices will be deemed exempt IVCTs
  - With certain exceptions, such as instruments (subject to grace period)
- IDEs will become investigational IVCTs

Submissions under review on VALID effective date will have their reviews completed under existing standards (i.e., 510(k), *de novo*, or PMA)

Breakthrough designations are not explicitly addressed

Transition Process, cont.

- VALID takes effect beginning the 4th fiscal year after enactment

- Qualifying LDTs offered before enactment will be grandfathered
  - But modifications trigger a new submission
  - Subject to FDA's "clawback" authority

- Qualifying LDTs first offered after enactment but before the effective date are "transitional IVCTs"
  - Transitional IVCTs may continue to be offered subject to filing a marketing submission within 90 days of the effective date

The VALID Act Timeline: Enactment to Implementation

	Year 1	Year 2	Year 3	Year 4
Enactment				
FDA Draft Guidance: • Third party accreditation • Collaborative Communities	**By 180 days**			
FDA Draft Guidance: • Near patient testing • Breakthrough				
FDA Final Guidance • Breakthrough				
FDA Third Party Accreditation				
FDA Public Meetings				
FDA Issue Regs • Adverse event reporting • Recalls • Adulteration and misbranding				
FDA draft, final guidance • Premarket review • Technology Certification				
Implementation				

Assessment

AdvaMedDx VALID Assessment Framework

Developed with member company regulatory experts, identifies and describes the highest priorities in diagnostics regulatory reform for IVDs; outlining additional policies of importance. Sets criteria for analyzing each priority in The VALID Act.

Top priorities include: **risk-based** nature of framework; policies allowing post-market **modifications** without additional review; appropriate consideration of **instruments**; and a **voluntary, streamlined review pathway that fosters innovation.**

Assessment Framework is serving as a roadmap for bill analysis by AdvaMedDx and member company experts.

Assessment Framework can be leveraged by member companies to determine impact of The VALID Act on their businesses.

AdvaMedDx: The VALID Act Assessment Framework								
Column 1	2	3	4	5	VALID Act (3/5/2020)			
Policy	**Description per VALID Draft (released 12/2018)**	**Priority Level (PL) (High, Mid, Low)**	**Priority Level Rationale**	**Criteria for Assessment**	**Equal Treatment for IVDs and LDTs (Yes/No)**	**Policy**	**Assessment using criteria in column 5**	**Potential Impact**
TOP PRIORITIES								
Applying a Risk-Based Framework	VALID uses risk as a key characteristic for determining review pathways for in vitro diagnostic tests whether LDT or IVD (referred to in the VALID draft as in vitro clinical tests, or IVCTs); not sole criterion.	**Highest**	Risk should serve as dominant determinate for IVCT regulation. A clear, predictable framework would incorporate appropriate review criteria and processes based on product benefit-risk balance that enables industry to readily understand regulatory category and the process to bring a product to market.	• Predictable framework with clear criteria for determination of high risk, high risk with mitigating measures, and low risk to enable predictability for IVCT developers on what IVCTs are subject to FDA review based on risk without automatic exclusions. • Associated, predictable regulatory pathways that are predominately determined by risk, subject to clear, consistent submission review criteria. Instruments that are currently low-risk or otherwise exempt from premarket review should maintain that status. • Clear risk-based patient and public health-focused criteria and procedures for changing the regulatory category or the		• Clarifies IVCT with MM is not high risk, but high risk definition tweaks need to be assessed (p. 9-10) • Definitions high risk, low risk, and MM have been tweaked and need to be evaluated (pp. 9-15) • Special pathway now clearly delineated; but needs clarification for certain test types (pp. 58-59). • Implies FOAK tests that are not high risk qualify for special pathway but process for	• Not solely a risk-based framework in light of automatic exclusions. • VALID adopted proposed language that IVCT is based on its own risk in component section but not elsewhere. VALID Regulatory Sub Team Group recommendation that we walk an accessory through the paradigm established by the bill to determine how the accessory would be regulated. • IVCT definition: Ensure that by	

AdvaMedDx VALID Assessment: Highest Priorities

Risk-Based Framework

Modifications

Instruments

Technology Certification
(formerly Precertification)

Transition

AdvaMedDx VALID Assessment: Risk-Based Framework

Description: The VALID Act uses risk as a key characteristic for determining review pathways for in vitro diagnostic tests (LDTs and IVD, collectively referred to in the draft as In Vitro Clinical Tests (IVCTs)

- Risk is not the sole criterion. Exemptions are not solely based on low-risk status.
- Provides two review levels, with certain IVCTs also eligible for the Technology Certification pathway.
- “Risk-based” priority is a compilation of many policies in the bill where risk should be appropriately considered when determining level of regulation.

AdvaMedDx VALID Assessment Framework: Modifications

Description: Changes to analytical or clinical validity generally require FDA review (with certain exceptions).

- FDA and IVCT test developers can agree upon change protocols during review.
- Allows modifications within protocol to be made without requiring premarket review of the modification.
- Other modifications subject to review.

AdvaMedDx VALID Assessment Framework: Modifications

Trending Positive; Further Improvements Needed

- **Preliminary Assessment**:
  - Modifications standards no longer turn on “notification elements” and instead focus on changes to analytical or clinical validity or intended use.
  - Modifications exempt from supplemental review include certain software updates, safety-related labeling changes, and changes to specimen stability.
  - Changes allowed within an approved change protocol; protocols are subject to annual reporting.
  - Scope of individual change protocol needs to be assessed, potentially further explained.
  - Manufacturing site change reviews broader than current approach.

VALID Assessment - Technology Certification

Description: Voluntary pathway for most IVCTs

- Allows advance marketing authorization for a suite of tests relying on the same technology.
- Categorically excluding several IVCT types (“Technology Certification”).
- Technology Certification applies to the range of tests defined by a particular technology.

VALID Assessment - Technology Certification

Preliminary Assessment: Secured Improvement; Further Improvement Needed

- Scope of certification is based on technology, as defined (e.g., flow cytometry, NGS), with examples provided in the definition.
- Categorically excluded IVCTs include instruments, specimen receptacles, home use, cross referenced tests, DTC, first of a kind, and high risk; FDA can qualify those that are underlined for eligibility.
- Technology Certification process and submission elements need to be scrutinized more closely; bill allows use of approved IVCT as a representative assay.
- Certification lasts up to 4 years; can be renewed.
- Appropriate scope and process for allowable modifications under a single certification order without additional review by FDA.

AdvaMedDx VALID Assessment Framework: Instruments

Description: Would require instruments to go through premarket review, but would only require review of one version of an instrument within an instruments family. Grace period for currently exempt instruments to undergo review.

- **Preliminary Assessment**: **Secured Improvement; Potential for Additional Improvement Modest**
  - Instruments (platforms) that are currently low-risk or otherwise exempt from premarket review would not maintain their exempt status, but approval of any instrument within an instrument family would cover other versions.
  - Instruments are subject to abbreviated review, only showing analytical validity.
  - Instruments are not eligible for Technology Certification.
  - Currently exempt instrument would have five years from enactment to undergo review.

AdvaMedDx VALID Assessment Framework: Instruments

Description:

- Would require instruments to go through premarket review.
- Would only require review of one version of an instrument within an instrument family.
- Grace period for currently exempt instruments to undergo review.

AdvaMedDx VALID Assessment Framework: Transition

Preliminary Assessment: <u>All Details New as Draft was Silent on Timeframes</u>

- The timelines for FDA to issue guidances and regulations during the transition period may not provide sufficient lead time for assessing the premarket review and Technology Certification pathways.
- Grandfathered LDTs (those introduced prior to enactment) would be exempt from review (subject to modifications) and would not list with FDA within one year after the effective date; provisions addressing LDTs that are transitional IVCTs (those introduced between enactment and the effective date) are not drafted clearly.
- Potential risk that grandfathering and transitional opportunities might lead to LDTs being rushed to market.
- User fees would be negotiated following existing MDUFA process, and would start soon after enactment; user fees would not be available, however, until FDA issued certain implementing guidances.

Gap Assessment: Key Areas of Improvement for The VALID Act Based on Initial Assessment

- **Risk-Based:** Further assessment of key definitions (high risk; mitigating measures; “first of a kind”; “well characterized”); certain types of IVCTs should not default into the “full review” (and be ineligible for Technology Certification); more flexible redesignation process needed for IVCTs to qualify for more favorable review pathways or exemptions.
- **Modifications:** Only **clinically meaningful** changes to an IVCT’s analytical or clinical validity should require FDA review; reporting of other changes should be pared down, particularly for changes within the scope of a change protocol; manufacturing site change reviews should be narrowed consistent with current approach for devices.
- **Voluntary Streamlined Pathway:** Technology Certification needs better approach to make excluded IVCT types eligible; definition of “technology” may need some refinement or assurances; submission elements for the certification application need to be evaluated further.

Gap Assessment: Key Areas of Improvement for The VALID Act Based on Initial Assessment

- **Instruments:** While adoption of an "instrument family" approach is helpful, would be preferable to maintain current exemption for low-risk instruments; under this approach, need to clarify that an existing IVD clearance with an instrument would qualify the instrument; finally, a longer grace period for currently exempt instruments is needed.

- **Transition:** Transition period and implementation timeline need to be assessed for impact on companies' regulatory strategies; grandfathering and transitional allowances for LDTs may inadvertently lead to introduction of tests not properly validated in order to fall within VALID's grace periods.

Continuing Assessment: Improvement for The VALID Act

Examples of additional areas to be assessed:

- Definitions
- Mitigating Measures
- POC
- CLIA Waiver
- Collaborative Communities
- Quality System
- Adverse Event Reporting
- Notification
- Submission Elements
- EUA
- Process for automatic exclusions

Next Steps

AdvaMedDx Board requested to utilize Assessment Framework to determine impact of VALID on your business. Impacts to be aggregated and presented at June board meeting.

AdvaMedDx and member company regulatory experts and government affairs professionals **continue detailed assessment of VALID,** pursuing clearly identified and agreed upon policy improvements on Hill.

In alignment with member companies, AdvaMedDx will encourage a thoughtful legislative process. A first key milestone of this process would be a **legislative hearing** in the House and then the Senate.

Engagement with the FDA. The agency will likely be asked by bill sponsors to develop Technical Assistance (TA) on VALID. AdvaMedDx will seek another round of "listening sessions" with the agency, as was done prior to introduction, to assess agency preference/ intent on key policies.

Stakeholder engagement, seeking alignment and collective action on the Hill to support diagnostics regulatory reform.

Media efforts to raise profile of dx regulatory reform emphasizing IVD priorities, breadth of stakeholder alignment, encourage movement of reform on the Hill. Planned Op-Eds with patient groups.

AdvaMedDx will seek changes to VALID in pursuit of IVD priorities that include ensuring the framework is appropriately risk-based, embraces innovation through modernized review pathways and applies policies equitably to LDTs and IVDs.

Questions?