The Verifying Accurate Leading-Edge IVCT Development (VALID) Act of 2021

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Agenda

- AdvaMedDx's Position on Dx Regulatory Reform
- Introduction of VALID 2021
  - Context
- VALID 2021: Overview
  - Important definitions and concepts
  - Framework
  - Key policies
  - Transition
- Assessment of Bill
- Next Steps

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.

Introduction of The VALID Act of 2021:

Context

June 24, 2021, The "Verifying Accurate Leading-Edge IVCT Development Act of 2021" (or "VALID Act 2021") was introduced in the Senate and House.

Senate sponsors: Sens. Michael Bennet (D-CO); Richard Burr (R-NC). Sen. Burr is Ranking Member of the Senate Health, Education, Labor and Pension Committee. In a 50-50 Senate, Burr will have considerable influence over MDUFA V, the most likely legislative vehicle for VALID.

House sponsors: Rep. Dianna DeGette (D-CO); Larry Bucshon, MD (R-IN), both members of the Energy & Commerce Co., that has jurisdiction over FDA matters.

Fully expect the Biden Administration to support comprehensive dx regulatory reform.

COVID puts a fine point on the public health importance of reform.

VALID Act 2021 includes AdvaMedDx-supported improvements to Technology Certification and other changes we recommended to make the bill more risk-based. Bill largely mirrors 2020 version.

Legislative process will allow AdvaMedDx to pursue member-driven modifications and improvements to the bill; committee action to launch; MDUFA V is targeted legislative vehicle in 2022.

VALID 2021 Overview: Important Definitions and Concepts

In Vitro Clinical Test (IVCT)	Includes both laboratory developed tests (LDTs) and traditional in vitro diagnostics (IVDs); also includes diagnostic-related software.
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.

Important Definitions

High-Risk

IVCTs for which when used as intended by developer, undetected inaccurate results would present 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, significant delay, or discontinuation of life-supporting or-sustaining treatment. A risk determination would take into account multiple factors about the history and clinical circumstances of the technology and intended use. Excluded from the definition of high-risk IVCTs are those for which mitigating measures are established to prevent, detect or otherwise mitigate these risks.

Low-Risk

IVCTs for which when used as intended by developer, undetected inaccurate results would cause minimal, no, or immediately reversible harm or disability, or only a remote risk of adverse patient or public health impact. That risk determination would take into account multiple factors about the history and clinical circumstances of the technology and intended use. Low-risk IVCTs also include those that would cause serious adverse health consequences, serious risk of adverse patient experience, and reversible (but not immediately) harm, but for which mitigating measures are capable of ensuring the test is low-risk.

Important Definitions

Mitigating Measures	Controls, standards or requirements determined by FDA to be necessary for an IVCT or category of IVCTs to meet their applicable standard or to mitigate risk of harm from an inaccurate result such that the IVCT or category of IVCTs is/are either not high risk or is/are low risk. These may cover labeling, conformance to performance standards or guidance, performance testing, advertising and promotion, clinical studies, submission of clinical data, user comprehension studies, postmarket studies, training, and availability of confirmatory laboratory or clinical findings.
Applicable Standard	A reasonable assurance of analytical and clinical validity for most IVCTs. For 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	An IVCT with both a different intended use and indications for use than any legally marketed IVCT. (*Note, FDA has identified a different concept for defining First of a Kind*)
Technology	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.

VALID 2021 Overview: Framework

- Comprehensive Test Information System and Registration & Listing
- Exempt Tests and Limitations on Exemptions
- Review Pathways:
  - Full premarket review
  - Special premarket review
  - Technology Certification
  - Breakthrough
  - Change Protocols
- Transition Process

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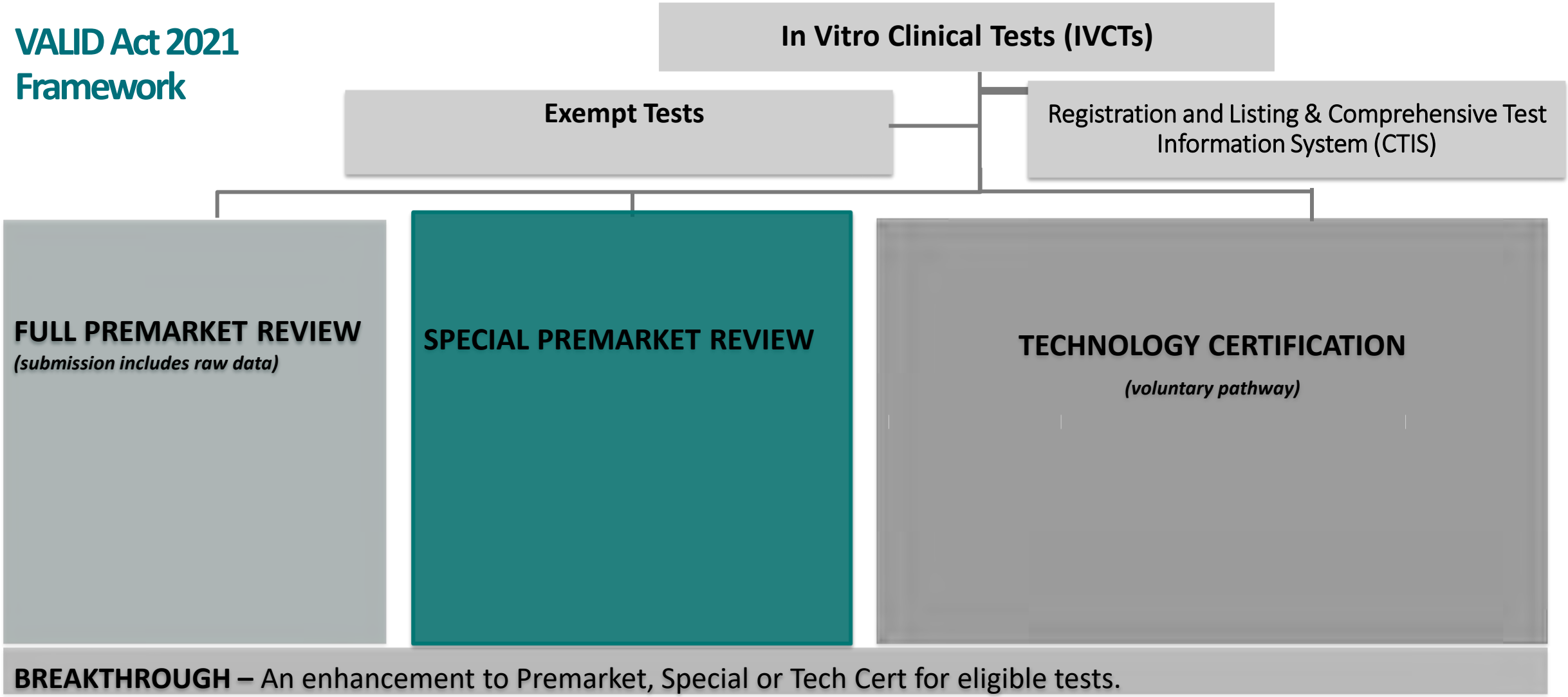
VALID Act 2021 Framework



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VALID Act 2021 Framework

In Vitro Clinical Tests (IVCTs)

Registration and Listing & Comprehensive Test Information System (CTIS) &

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.)

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, adverse event reports, 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.

VALID Act 2021 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
- Tests introduced under a Technology Certification
- Investigational use tests

VALID Act 2021 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~~

VALID Act 2021 no longer requires these categories of tests to automatically go through full premarket review.

SPECIAL PREMARKET REVIEW

("Special pathway")

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.
- 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.
- ***VALID Act 2021 no longer automatically excludes certain test types (Cross-Referenced, First of a Kind, Direct to Consumer, Home Use), from eligibility.***

BREAKTHROUGH

CHANGE PROTOCOLS

(modifications otherwise subject to review if they affect analytical or clinical validity)

Positive change: VALID 2021 removed prior version's restrictions

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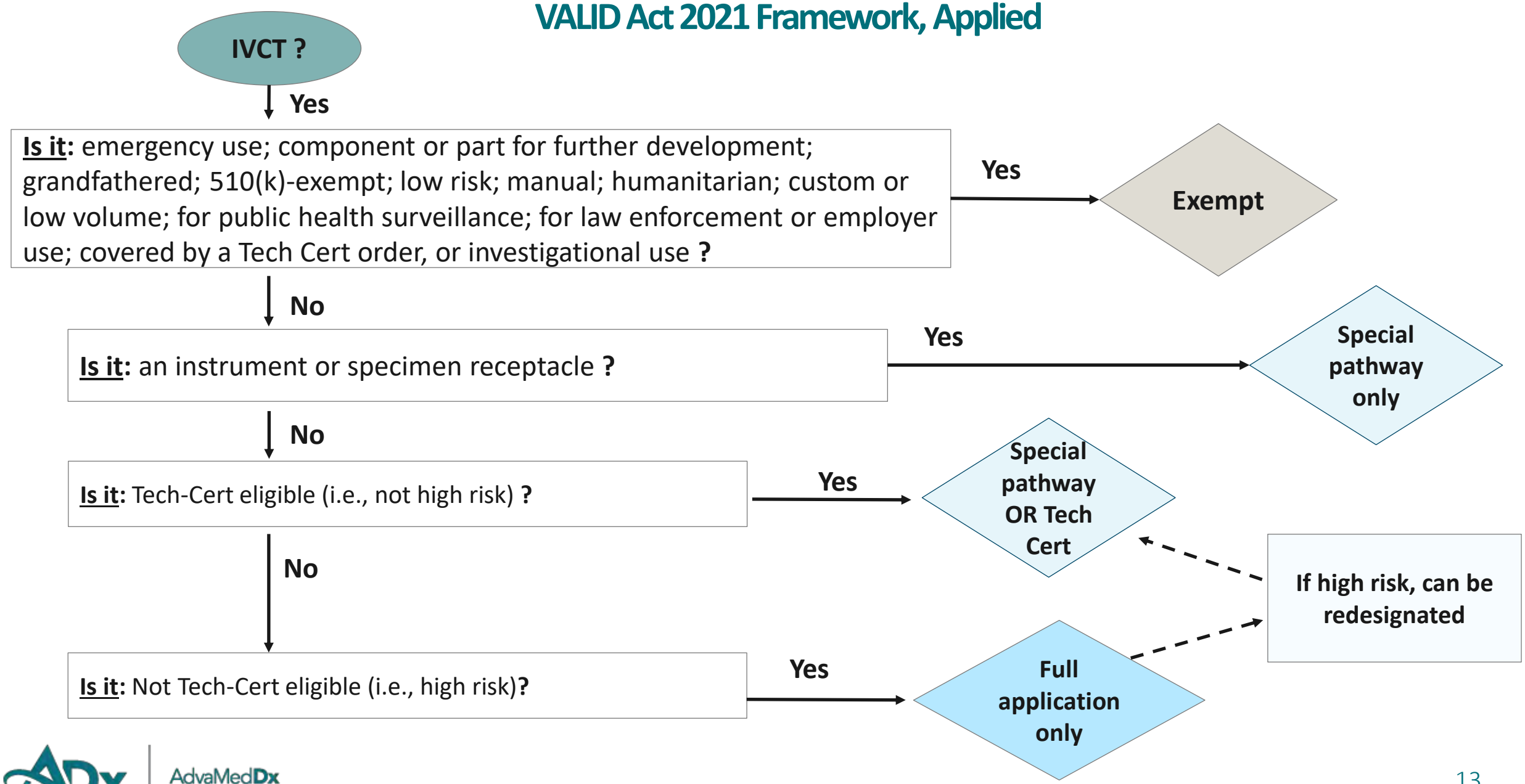
VALID Act 2021 Framework, Applied



VALID Act 2021 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": 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": 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 for 4 years; Unlimited number of subsequent Tech Certs for 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 2021 Overview: Key Policies

- Clinical Laboratory Improvement Amendments (CLIA)
- Quality requirements
- Recognized standards
- Labeling
- Adverse event reporting
- Adulteration
- Misbranding
- Remedies
- Collaborative Communities
- Additional policies

VALID Treatment of Clinical Laboratory Improvement Amendments (CLIA)

CLIA	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 (e.g., validation, notification).
	Registration and listing: Required elements include CLIA certificate number.
Grandfathering	Qualifying LDTs would be eligible for grandfathered status subject to FDA "claw-back" authority; grandfathered tests could not be modified without being subject to review by FDA.

VALID Treatment of CLIA, cont.

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 & Medicaid Services (CMS) under CLIA. Establishes different quality requirements for labs that are and are not CLIA-certified for high-complexity testing. Directs FDA to 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.
Emergency	
	Generally,

Quality Requirements	VALID establishes test design and 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 the 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 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.

Additional Policies	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 exception, such as instruments (subject to a 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	Existing designations are not explicitly addressed

Transition Process, cont.

VALID takes effect 4 years 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 [prior to] the effective date *(the language is somewhat unclear on the required timing of the submission and how long it may stay on the market).*

VALID Act 2021 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 • Tech Certification • Premarket review (587B)				
FDA draft, final guidance • Applicability (587A)				
Implementation				

Assessment of VALID

Assessment Tool: 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 VALID Act 2021.

Top priorities include **risk-based** nature of framework; policies allowing **post-market modifications** without additional review; and a voluntary, streamlined review **pathway that fosters innovation ("Technology Certification")**.

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 VALID Act 2021 on their businesses.

AdvaMedDx VALID Assessment: Highest Priorities

1. Risk-Based Framework advances made; additional improvements sought

2. Modifications

3. Technology Certification significant advances made

4. Transition

VALID Assessment:

1. Risk-Based Framework

General description: VALID Act 2021 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).

Favorable revisions to Tech Cert removing automatic exclusions, first-of-a-kind, and special pathway eligibility consistent with risk-based approach.

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.

Advances made; additional clarity sought:

Further assessment of revised key definitions (high risk; low-risk; mitigating measures) and application requirements.

VALID Assessment:

2. Modifications

General 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.

- A few categories of modifications, e.g., appropriate safety labeling updates, exempt from premarket review of the modification Other modifications subject to review.

Preliminary Assessment: Virtually no changes made from 2020 version. Modifications exempt from supplemental review include certain software updates; appropriate safety-related labeling changes; 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 review broader than current approach.

Concept included; improvements sought:
*Only **clinically meaningful** changes to an IVCT's analytical or clinical validity should require FDA review; reporting of other changes should be pared down; manufacturing site change reviews should be narrowed.*

VALID Assessment:

3. Technology Certification

General description: Geared to foster innovation, this voluntary pathway is for vast majority of IVCTs subject to review. Ineligible are high risk tests without mitigating measures.

- Allows advance marketing authorization for a suite of tests relying on the same technology.
- No longer categorically excluding several IVCT types ("Technology Certification").
- Technology Certification applies to the range of tests defined by a particular technology.

Preliminary Assessment:

- Scope of certification is based on technology (as opposed to narrower, "medical specialty" approach), with examples provided in the definition, i.e., flow cytometry, NGS.
- Importantly, VALID 2021 removes 2020's categorical exclusions (home use, cross-reference tests/CDx, direct-to-consumer, first of a kind, and high-risk). Categories would be eligible for Tech Cert.
- Certification to last 4 years (as opposed to up to 4 years); can be renewed.
- Appropriate scope and process for allowable modifications under a single certification order without additional review by FDA.

Significant improvements secured. This pathway is likely subject to change in the legislative process.

VALID Assessment:

4. Transition

General description: Takes effect 4 years after enactment.

Preliminary Assessment:

- VALID 2021 added two-year deadline to issue final guidance regarding applicability (587A);

- VALID 2021 appears to add a tight, two-year deadline to issue final regulations (instead of guidance in prior version) regarding premarket review (587B) and Technology Certification (587D).

- Grandfathered LDTs would be exempt from review 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*. *Note: this appears to be a drafting error as the referenced documents are now regulations, and a conforming change is needed.*

Clarity needed on several policies herein given drafting ambiguities. Improvements needed to ensure *grandfathering and transitional allowances for LDTs may not inadvertently lead to introduction of tests not properly validated in order to fall within VALID's grace periods.*

Continuing Assessment: Improvement for VALID Act 2021

VALID Assessment:

Examples of additional priority policies:

- Point-of-Care / CLIA Waiver

AdvaMedDx has developed detailed language to improve policy in VALID

Definitions:

- EUA.
- Collaborative Communities.
- Quality System.
- Adverse Event Reporting.
- Notification.
- Submission Content (i.e. for Special Pathway and Tech Cert).

AdvaMedDx has developed member-driven policy improvements for each of these areas and others.

Next Steps

AdvaMedDx and member company regulatory experts and government affairs professionals **continue detailed assessment of VALID 2021, to guide** improvements to the bill to further the interest of the IVD industry, accelerating patient access to quality diagnostics.

July, onward: In alignment with member companies, AdvaMedDx will encourage a thoughtful legislative process. To encourage House & Senate Committee engagement we will build **cosponsorship**. Cosponsorship ≠ endorsement. Prepare for fall potential **legislative hearing** in the House.

July/August: Engagement with the FDA. The Agency has provided Technical Assistance (TA) on VALID 2020 to the Hill. AdvaMedDx will seek another round of "listening sessions" with the Agency to assess Agency preference/intent on key policies.

End-July, onward: Stakeholder engagement. AdvaMedDx and ACLA-led broad stakeholder group engagement for collective action on the Hill to support diagnostics regulatory reform (letters; cosponsors).

July onward: Media efforts to raise profile of dx regulatory reform emphasizing IVD priorities, breadth of stakeholder alignment, encourage movement of reform on the Hill.

Seek to solidify VALID by ~ end of Q1 2022 so it is well-positioned with support from House & Senate Committees and the Administration to be considered a "rider" on the user fee reauthorization package, MDUFA V. MDUFA V, one of the user fees requiring Congressional authorization, will be finalized on the Hill ~Q3 2022.

Member Resources

The VALID Act: A copy of the legislation is available **here.** A summary of the bill, prepared by bill sponsors, is available **here**.

AdvaMedDx VALID Assessment Framework: The **Assessment Framework**, developed with member company regulatory experts, prioritizes issues of importance for the IVD industry, setting forward the criteria we are using to assess the key policies in the bill. As our analysis continues, the framework will continue to be updated. Contact Jamie Wolszon for latest version, **jwolszon@advamed.org**

Dx Regulatory Reform 101: This AdvaMedDx **fact sheet** is designed for use on the Hill and with stakeholders to outline the rationale for modernizing the regulatory framework for all in vitro clinical tests (LDTs and IVDs) for clinical use.

VALID FAQs for Media Inquiries: AdvaMedDx has prepared a high-level **FAQ** document that addresses key questions you may receive about the bill. We anticipate updating this document following additional analysis of the legislation.

Repository of AdvaMedDx-developed, VALID-related Documents: Summary of top priorities; legislative redlines; narrative description of redlines; numerous and detailed supporting documents, and more. Documents go back to January 2020 and are available here: **0- JWolszon- Documents Submitted to VALID Sponsors January 2020- May 2021**

Questions?

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