



Current Proposals for Diagnostics Reform

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Diagnostic Reform

Elizabeth Hillebrenner

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May 3, 2019

Laboratory Developed Tests (LDTs)

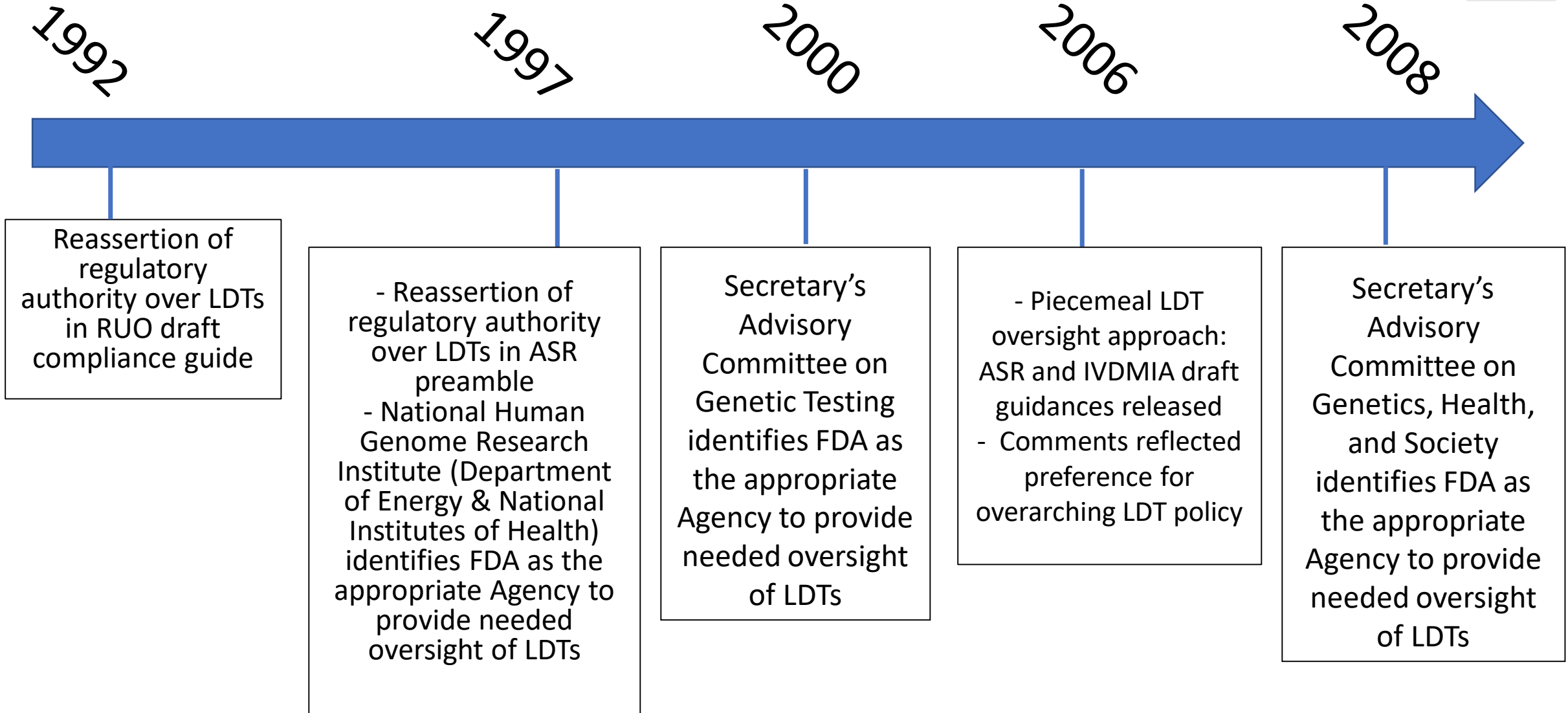
1976

- FDA exercised enforcement discretion for LDTs because they were generally:
 - simple, relying on manual techniques used by lab personnel
 - run in small volumes by local laboratories with shared responsibility for patient outcomes
 - assembled using components legally marketed for clinical use

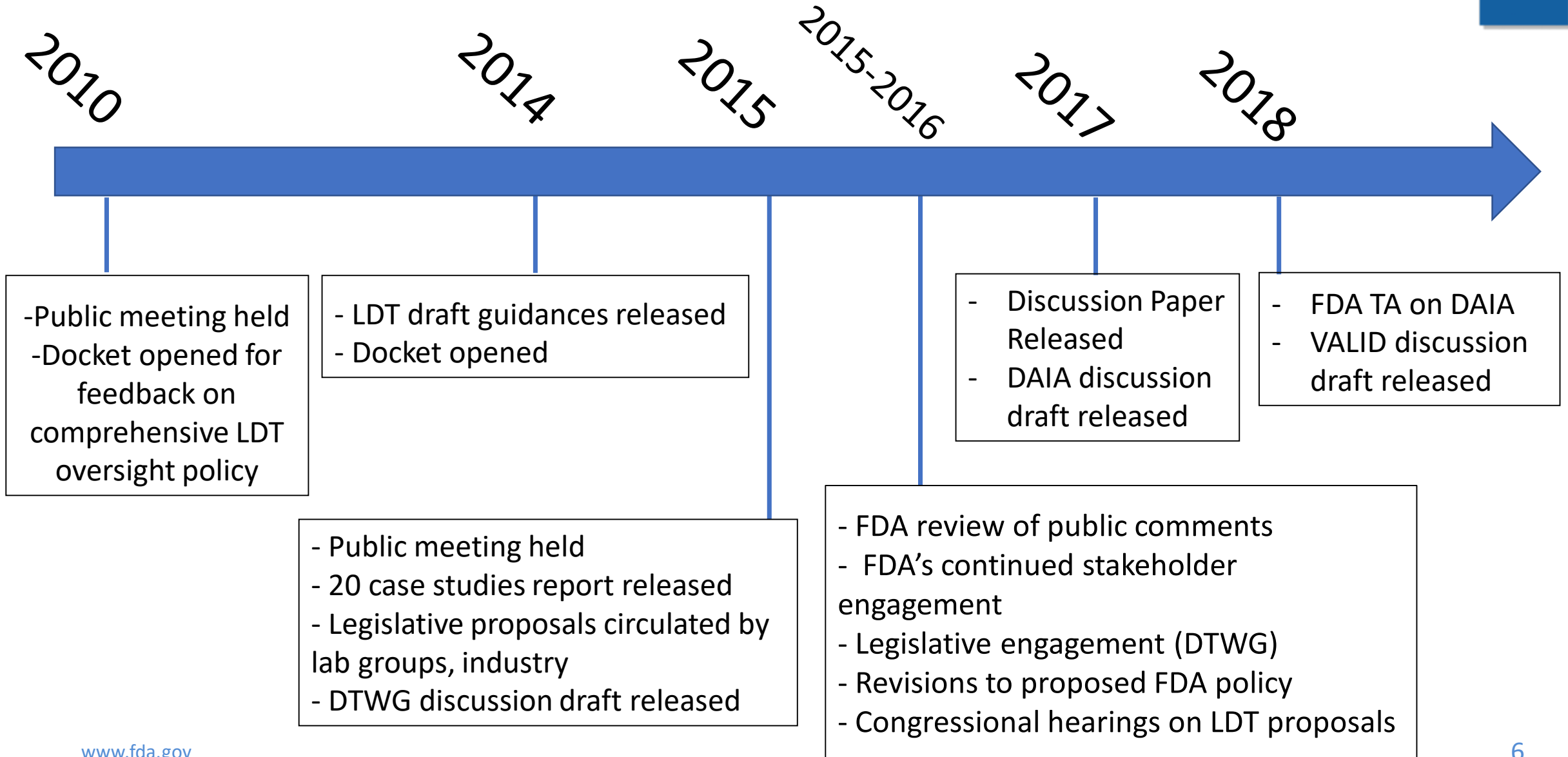
Today

- The landscape has evolved such that increasingly we are seeing LDTs that are:
 - more complex, sometimes including black box algorithms
 - run in large volumes as reference labs for patients from different institutions around the world
 - assembled using components intended for research use only

LDT History



LDT History





FDA's August 2018 Technical Assistance

- New medical category: In Vitro Clinical Tests (IVCTs) includes LDTs and conventional IVDs
- New framework tailored to IVCTs
 - FDA jurisdiction, complementary to CLIA
 - Reasonable assurance of analytical and clinical validity (AV and CV)
 - No formal classification process; focus on where our review adds most value (e.g., high risk, novel)
- Premarket oversight:
 - ~50% exempt
 - ~40% eligible for precertification (or abbreviated premarket review)
 - ~10% subject to individual premarket review
 - Streamlined approach to modifications
- Postmarket oversight:
 - Special Rule
 - Transparency
 - Adverse event reporting
 - General authorities (e.g., recalls, corrections and removals)
- QS leverages CLIA where appropriate

Exemptions

Category	Notification	PreMarket Review	QS	AE Reporting	Labeling
Grandfathered		Exempt	Exempt		Exempt*
Pre-certified		Exempt			
Low risk		Exempt			
Exempt pre-enactment		Exempt			
Rare disease		Exempt			
Custom	Exempt	Exempt	Exempt		
Low volume	Exempt	Exempt	Exempt		
PH surveillance	Exempt	Exempt	Exempt	Exempt	Exempt
Law enforcement	Exempt	Exempt	Exempt	Exempt	Exempt
Manual	Exempt	Exempt	Exempt	Exempt	Exempt
Investigational	Exempt	Exempt	Exempt	Exempt	Exempt*

*specific disclaimer required

Precertification

- Voluntary alternative to premarket review for many IVCTs
- FDA would evaluate test developers to determine if their processes for development and validation will result in analytically and clinically valid tests
 - Full review of single representative assay to confirm
- Precertification scope:
 - Single technology and applicant-specified medical specialties
 - Not limited by intended use – a single precertification could include many different intended uses/test groups
- Eligibility
 - Developer must be in good standing
 - Tests that are first of a kind, cross-referenced, high risk, for home use or direct-to-consumer must be made eligible by FDA through regulatory pathway designation process
 - Other tests, with certain exceptions, are automatically eligible
- Once pre-certification is granted, new and modified eligible tests can be marketed without individual premarket review
- Recertification requirements

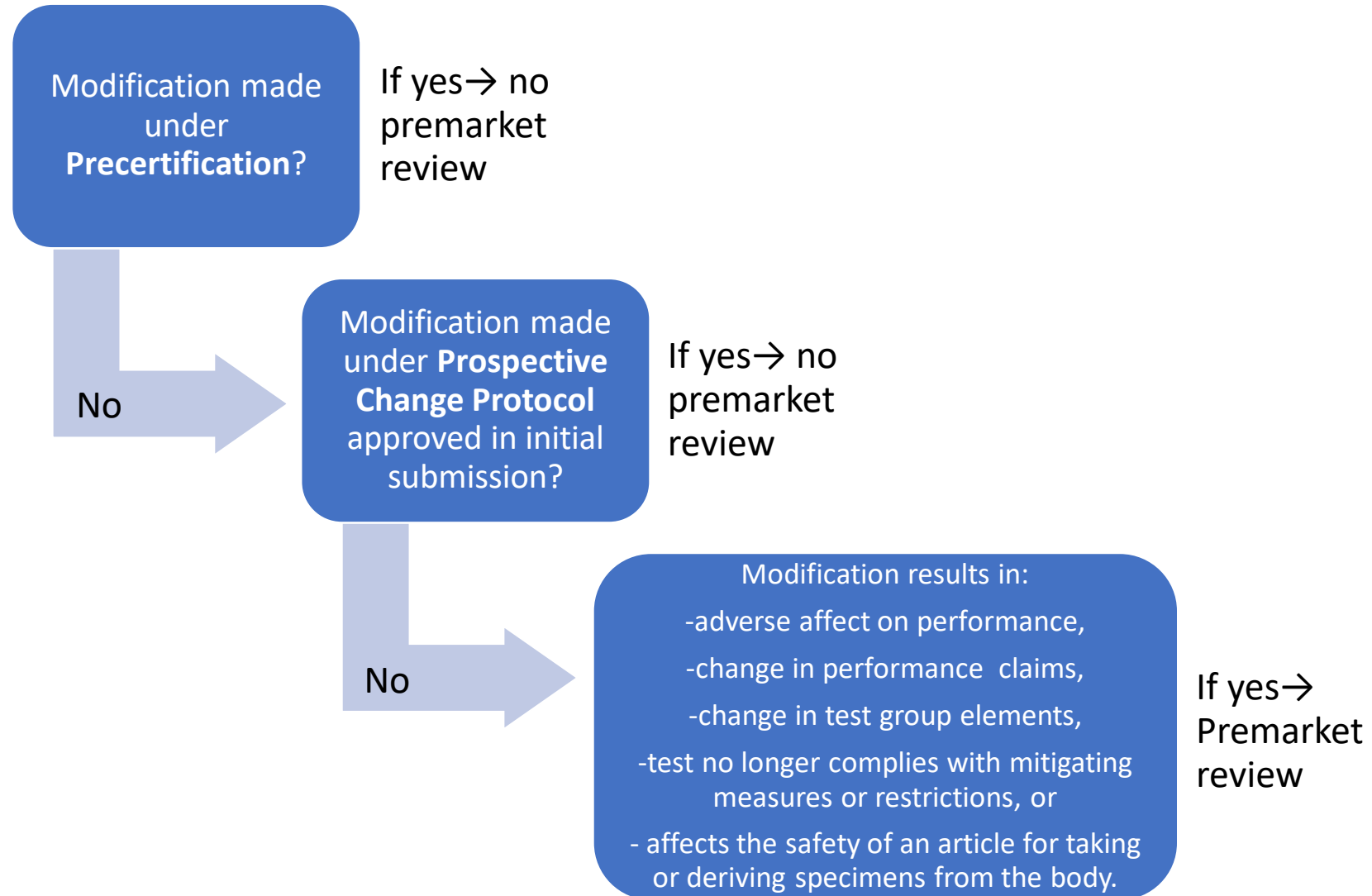
Premarket Review

	Analytical Validity Review	Clinical Validity Review	QS
Tests ineligible for precertification	Raw data	Raw data	Premarket review and inspection
Tests eligible for precertification	Summary data	Summary data	_*
Platforms	Summary data from representative assay	-	_*
Collection articles	Summary data from representative assay	-	_*

*While QS may not be reviewed premarket, all IVCTs would be subject to QS requirements, unless exempt, and documentation should be available upon request or routine inspection

Note: The data demonstrating analytical and clinical validity of a single assay could be used for any combination of the following: a premarket submission for the assay, a precertification for all eligible assays using the technology, a premarket submission for the platform, and a premarket submission for the collection article; data would need only be submitted once

Modifications



Transparency

- Comprehensive Test IT System (CTIS) would include:
 - Registration of developers and related entities
 - Notification of individual IVCTs with public transparency performance summaries
 - Electronic submission portal
 - Adverse event reporting portal
 - Identification of regulatory pathway for non-novel test groups
- CTIS would enable efficient oversight by FDA
 - Monitoring of all tests, including those introduced under precertification and the developer's claims associated with them
- CTIS would provide transparency to patients and healthcare providers about the tests they are using
 - Ability to search for available tests based on any individual elements of a test group
 - Ability to compare performance of similar tests

Special Rule

- The shift away from premarket review for most tests necessitates clear, workable postmarket monitoring and enforcement authorities
- FDA must have the ability to address problematic IVCTs, including those that may be grandfathered
- The process would involve FDA first asking for more information, and if a finding was made based on that information, we could request that the developer provide a submission, or we could remove the test from the market, depending on the nature of the finding.
- In order to protect the public health, FDA would **only** invoke the special rule if:
 - There is insufficient VSE to support AV or CV (different rule for specimen collection articles)
 - Materially deceptive or fraudulent analytical or clinical claims
 - Reasonable potential the IVCT will cause death or serious adverse health consequences

Transition Period

- The period between the enactment date and the implementation date (applicability)
- Transition is needed for FDA to prepare the necessary infrastructure, issue any necessary guidances, and provide training on the new program
- LDTs during transition
 - Any LDTs introduced 90 days prior to the enactment date would be grandfathered
 - LDTs introduced between 90 days prior to enactment and the implementation date would be transitional IVCTs and may need a premarket submission after the implementation date (unless otherwise exempt)
 - Transitional IVCTs subject to delayed premarket review could continue to be offered for clinical use during the pendency of review to ensure no market disruption
- Conventional IVDs during transition
 - Conversion of existing approval/clearance/authorization – any IVD with an FDA approval, clearance, authorization, or licensure before the enactment date would be deemed to have an approved application after the effective date
 - Authorization during transition – IVD manufacturers would continue to seek FDA authorization under the device regulations until the implementation date, at which time such would be converted to an approval



VALID

FDA looks forward to continued engagement, at the direction of Congress, as we all work toward a legislative solution that will ensure patients have access to analytically and clinically valid in vitro clinical tests when they need them.

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[Discussion Draft]

[PRELIMINARY DISCUSSION DRAFT]

115TH CONGRESS
2D SESSION

H. R. _____

To amend the Federal Food, Drug, and Cosmetic Act to provide for the regulation of in vitro clinical tests, and for other purposes.

IN THE HOUSE OF REPRESENTATIVES

Mr. BUCSHON (for himself and Ms. DEGETTE) introduced the following bill; which was referred to the Committee on _____

A BILL

To amend the Federal Food, Drug, and Cosmetic Act to provide for the regulation of in vitro clinical tests, and for other purposes.

1 *Be it enacted by the Senate and House of Representa-*
2 *tives of the United States of America in Congress assembled,*

3 **SECTION 1. SHORT TITLE; TABLE OF CONTENTS.**

4 (a) **SHORT TITLE.**—This Act may be cited as the
5 “Verifying Accurate Leading-edge IVCT Development Act
6 of 2018” or the “VALID Act of 2018”.

7 (b) **TABLE OF CONTENTS.**—The table of contents of
8 this Act is as follows:

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December 6, 2018 (3:04 p.m.)



Current Proposals for Diagnostics Reform

**Eric M. Marshall, Senior Director,
Leavitt Partners LLC**

	Historical Medical Device Framework	FDA Draft Guidance (2014)	DAIA (2017)	VALID (2018)
Premarket Requirements for LDTs	<ul style="list-style-type: none"> FDA enforcement discretion Not subject to medical device requirements or other FDA oversight 	<ul style="list-style-type: none"> Medical device requirements for premarket review extended to LDTs Reasonable assurance of safety and effectiveness as approval standard Risk-based classification based on the availability of controls using existing medical device classification system 	<ul style="list-style-type: none"> Creates new category under FDCA for in vitro clinical tests (IVCTs) Reasonable assurance of analytical and clinical validity established as standard for approval Adopts risk-based classification system based upon patient risk 	<ul style="list-style-type: none"> Creates new category under FDCA for in vitro clinical tests (IVCTs) Reasonable assurance of analytical and clinical validity established as standard for approval, and safety as applicable
Premarket Requirements for IVDs	<ul style="list-style-type: none"> Regulated as medical devices subject to all classification, premarket, and other device requirements 	<ul style="list-style-type: none"> No significant changes to medical device requirements as applied to IVDs 	<ul style="list-style-type: none"> Premarket review for high-risk IVCTs Streamlined submissions for moderate-risk IVCTs Registration and listing for low-risk IVCTs 	<ul style="list-style-type: none"> Attempts to eliminate risk-based classification, establishing 2 to 4 classes Creates voluntary precertification pathway
Special Pathways	<ul style="list-style-type: none"> Standard device pathways available 	<ul style="list-style-type: none"> Continued enforcement discretion for LDTs for: <ul style="list-style-type: none"> Unmet need LDTs Rare disease LDTs “Traditional” LDTs 	<ul style="list-style-type: none"> Establishes expedited “approval with confirmatory post-market obligations” pathway for unmet need and clinically significant advantage 	<ul style="list-style-type: none"> To-be-defined alternative pathway for breakthrough IVCTs and IVCTs that provide a clinically meaningful advantage
Post-Market Obligations	<ul style="list-style-type: none"> IVDs regulated as medical devices subject to all post-market requirements LDTs not subject to FDA post-market requirements 	<ul style="list-style-type: none"> Medical devices post-market requirements extended to LDTs, including adverse event reporting, corrections and removals, and modification requirements 	<ul style="list-style-type: none"> Tailored modification requirements based on changes to intended use or meaningful clinical impact Quarterly adverse event summary and trend reporting 	<ul style="list-style-type: none"> Device-like post-market requirements with some summary reporting
CLIA	<ul style="list-style-type: none"> Test services regulated by CLIA 	<ul style="list-style-type: none"> No changes to CLIA 	<ul style="list-style-type: none"> Harmonizes CLIA and FDA requirements Modernizes CLIA requirements to CAP standard 	<ul style="list-style-type: none"> No changes to CLIA Instructs FDA to avoid duplicative requirements



Current Proposals for Diagnostics Reform

Aaron L. Josephson, Senior Director, ML
Strategies LLC

- Elizabeth: brief history followed by overview of FDA TA & VALID Act

- Eric: DTWG proposals/history

ACLA Response to VALID

1. Diagnostics are services and should not be regulated as or like medical devices
2. Legislation should allow for grandfathering and transitional tests so as not to disrupt patient access
3. Model should balance regulatory oversight with innovation

ACLA represents labs, whose tests have been subject to FDA enforcement discretion.

Service vs. Product

1. Diagnostics are services and should not be regulated as or like medical devices
 - To that end, ACLA proposes:
 - Separate FDA Center to regulate diagnostics or separate office with management and staff with experience specific to labs
 - “An LDT is essentially a service, while an IVD is a tangible product.”
 - Based on latest VALID Act, Congress does not agree with these positions

Patient Access

2. Legislation should allow for grandfathering and transitional tests so as not to disrupt patient access

To that end, ACLA proposes:

- 5 year default transition period between enactment and effective date unless regulations are promulgated earlier
- No lab tests should be subject to device provisions at any time
- Support for grandfathering of tests performed in a CLIA-accredited high-complexity laboratory under common ownership with the high-complexity lab in which the IVCT was developed
- There is too much discretion given to FDA to begin oversight of grandfathered tests if the agency has “reason to believe” there is insufficient evidence to support analytical and clinical validity
 - The burden should be on FDA to show that the test does not meet standards of analytical and clinical validity
- Modifications to grandfathered tests should be limited to modifications with a significant clinical impact or that change the intended use

Balance Oversight and Innovation

3. Model should balance regulatory oversight with innovation

- To that end, ACLA proposes:
 - Better delineation between CLIA requirements and QSR
 - VALID excludes lab operations from quality system requirements but should be excluded from the entire Act
 - ACLA agrees that summary information generally will be sufficient to support approval of most tests but language in VALID granting FDA significant discretion to require raw data could limit innovation by creating uncertainty for the type of data needed to support approval
 - Scope of precertification should not be limited to a single technology

AdvaMedDx Response to VALID

1. Clarification of terms
2. Technical changes that appear consistent with intent
3. Precertification should include multiple technologies (same as ACLA)

AdvaMedDx represents IVD manufacturers, who have been subject to FDA regulation and want to see all diagnostics regulated consistently regardless of where the test is developed.