Proposal for Modernization of CLIA Regulations for Laboratory Developed Testing Procedures

Expertise that advances patient care through education, innovation, and advocacy.

www.amp.org

AMP Association for Molecular Pathology

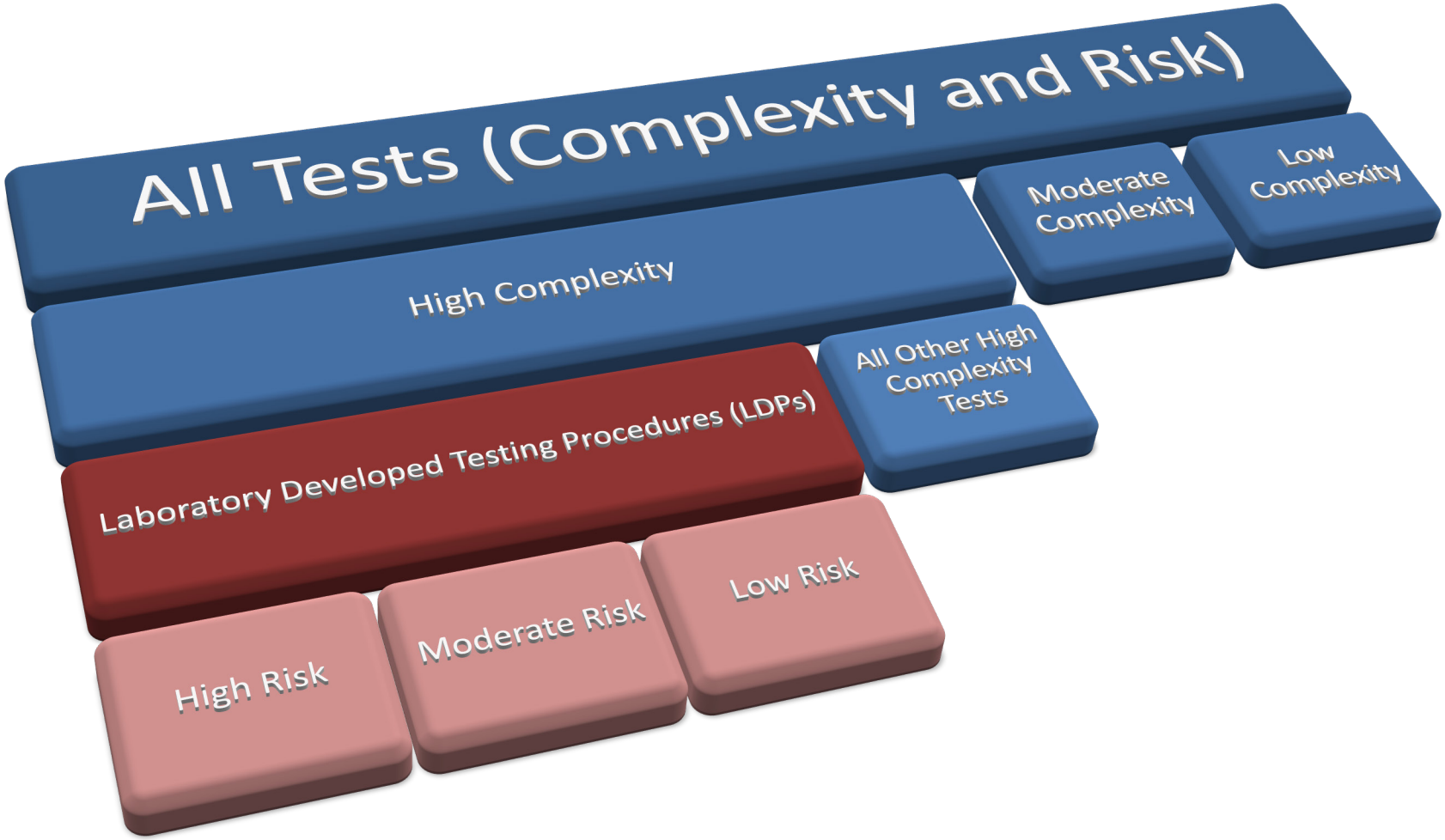
Desired Outcomes

- ✓ Patients receive the most appropriate test for their clinical condition
- ✓ Laboratory developed testing procedures (LDPs) are accurate, precise, clinically relevant, and monitored for continued quality performance
- ✓ Health care professionals able to provide professional services without undue restrictions
- ✓ Preserve the ability of the laboratory community to provide surge capacity in public health emergencies
- ✓ Regulatory oversight does not slow innovation, constrain flexibility and adaptability, or limit a test's sustainability
- ✓ Burdens on CMS are kept as minimal as possible; the use of third party organizations is strengthened

Rationale

- The field has grown and evolved significantly since the Clinical Laboratory Improvement Amendments (CLIA) of 1988 were enacted
- Diagnostic services are a professional healthcare activity and healthcare services are within the purview of CMS
- LDPs are fundamentally distinct from distributed test kits
- Separating oversight of laboratory-related activities would result in inefficient, burdensome, and duplicative regulations
- The proposal is a streamlined, cost-effective approach to addressing clinical validity and other issues
- Updating CLIA regulations preserves and strengthens the use of third party organizations

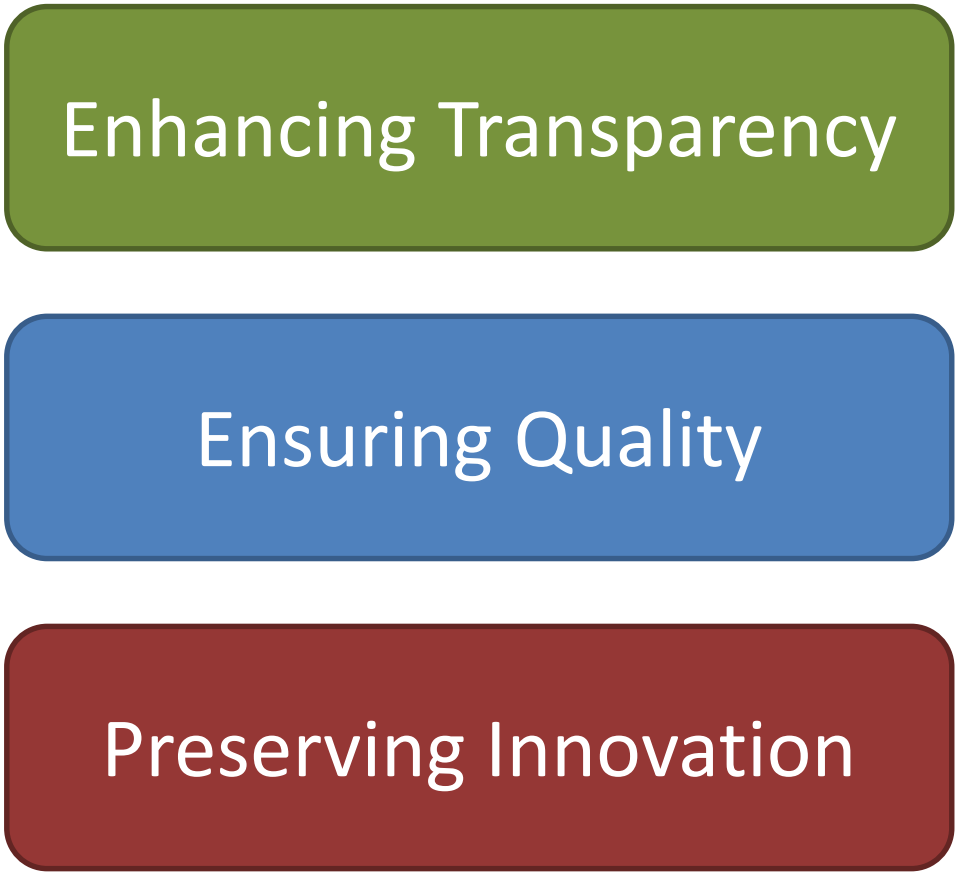
Proposal Applies to LDPs



Expertise that advances patient care through education, innovation, and advocacy.

www.amp.org

AMP Association for Molecular Pathology



The proposal is built on three major pillars

Key Features

- Tiered; risk-based
- Regulates LDPs as professional services
- Assures both analytical and clinical validity without jeopardizing innovation
- Provides for rapid response during public health emergencies
- Provides transparency so physicians and patients have essential information
- Levels the playing field by applying the same regulatory principles to anyone who develops an LDP
- Provides for pre-introduction review of high & moderate risk LDPs
- Provides for enhanced standards
- Requires proficiency testing or alternative assessment for all LDPs
- Does not change states' exempt status under CLIA
- Avoids duplication of activities within and between federal agencies
- Provides for shared LDP protocols
- Timeline: 2 years to final rule; another 2 years after final rule to take effect

LDP Submission and Publication Requirements

Enhancing Transparency

LDP Standardized Format

- CMS will develop a standardized format for information on LDPs – information will include:
  - LDP description (*i.e.*, claims, indication for use, intended use)
  - Analytical validity summary data (for publication)
  - Analytical validity full data (for review)
  - Clinical validity summary data (for publication)
  - Clinical validity full data (for review)
    - until relevant validity databases/aggregated evidence established
  - LDP methodology/technology
  - The date the test was put into service
  - Contact information for the laboratory
  - Certification/licensure number for the laboratory
  - Risk classification of the LDP

Submission & Publication Process

Laboratories will have to…

- Adopt the standardized format
- Submit the LDP information to CMS/Third Party Reviewer
  - Must be submitted before the LDP is introduced into clinical service as follows:
    - High risk: 90 days
    - Moderate risk: 30 days
      - Moderate risk LDPs introduced prior to 4/24/2003 exempt from publication & review requirements
    - Low risk: Exempt

Enhancing Transparency

- Laboratories will also have to make the LDP form readily available, *e.g.*, upon request, and provide instructions on how to access the information in any marketing materials

- CMS will be instructed to develop and continuously update a searchable database containing entries for all LDPs using LDP information submitted to CMS
  - New and updated information will be incorporated into the database within 30 days of CMS receiving it

LDP Review Requirements

Ensuring Quality

Preserving Innovation

Review of LDP Information

- CMS will develop a minimum level of standards
  - Must utilize Advisory Board of specialty subject matter experts
- CMS/Third Party Reviewer will review the LDP form within:
  - High risk: 90 days
  - Moderate risk: 30 days
    - Moderate risk LDPs introduced prior to enactment are exempt from review
  - Low risk: Exempt
- No required validity differences for high vs moderate risk LDPs
- The LDP is presumptively approved if CMS/Third Party Reviewer does not issue a decision within the time limit
- CMS may reclassify the risk during review
- CMS required to establish an appeal mechanism

Proprietary Information

- CMS is allowed to request and review proprietary information
- Labs may choose to submit their LDPs to FDA rather than provide proprietary information to CMS/Third Party Reviewers
- Third Party Reviewers will not be required to review High Risk LDPs

Clinical Validity

- Evidence may include a variety, including:
  - peer reviewed literature
  - clinical practice guidelines
  - bench studies, including use of archived specimens
  - consensus standards
  - data registries, *e.g.,* ClinGen, ClinVar, CancerLinQ, or other curated relevant databases
  - post-market data
  - clinical trials, including those conducted outside of the U.S.
- Once aggregated evidence is identified, subsequent submissions may simply reference that information

LDP Risk Classification

Classification	Definition
Low	An LDP for which the laboratory makes no claim that the test result alone determines diagnosis, prognosis or direction of therapy, absent other clinical information or diagnostic procedures, OR; the consequence of an incorrect result or interpretation is unlikely to lead to serious morbidity or mortality, either for the patient or the public health. LDPs used for rare diseases, for public health emergencies, and for infectious agents that are not serious threats to the public health are classified as low-risk.
Moderate	Taking medical context into consideration, an LDP that is used to diagnose a disease, predict risk of disease, or risk of progression of a disease, or patient eligibility for a specific therapy to treat a disease, that is associated with significant morbidity or mortality, AND; the test lends itself to inter-laboratory comparisons or proficiency testing.
High	Taking medical context into consideration, an LDP that is used to diagnose a disease, predict risk of disease, or risk of progression of a disease, that is associated with significant morbidity or mortality, AND; uses methodologies that involve proprietary algorithms or computations such that the test results cannot be tied to the methods used or inter-laboratory comparisons cannot be performed.

LDP Oversight Summary

Risk Classification	Low	Moderate	High
Submission	Exempt; Laboratory validates and puts into service	LDP information submitted at least 30 days before the LDP is offered to the public	LDP information submitted at least 90 days before the LDP is offered to the public
Review	Exempt	LDP reviewed (30 day time limit)	LDP reviewed (90 day time limit)
Evidence for Clinical Validity	N/A	Submit to reviewer as part of review packet	Submit to reviewer as part of review packet; CMS/Third Party Reviewer may require a clinical trial (only in some instances)
Proprietary Information	N/A	N/A	Lab must disclose proprietary information to reviewer only
Grandfathering	N/A	Yes	No
Exemptions	All exempt	Some exemptions	Some exemptions

"Grandfathering"

Moderate Risk	• Introduced prior to enactment: exempt from LDP Review (subject to LDP Publication requirements only) • Introduced prior to April 24, 2003: exempt from both LDP Review & Publication requirements
High Risk	No grandfathering: Subject to both LDP Review & Publication requirements

Other Exemptions

- LDPs used solely for public health surveillance (*i.e.*, not for clinical purposes)
- All LDPs that have approval from a state that has exempt status under the CLIA regulations and that requires pre-introduction review of analytical and clinical validity data will be exempt from the LDP Review requirements
  - *i.e.*, LDPs with NYS approval would not have to submit under CLIA regulations, but would only have to submit summary info to publish
- Compassionate use; LDPs offered to single patients with suspected or established serious or immediately life threatening condition
  - Ordering physician must be notified that LDP has not been approved and sign off on compassionate use

Conditional Approval

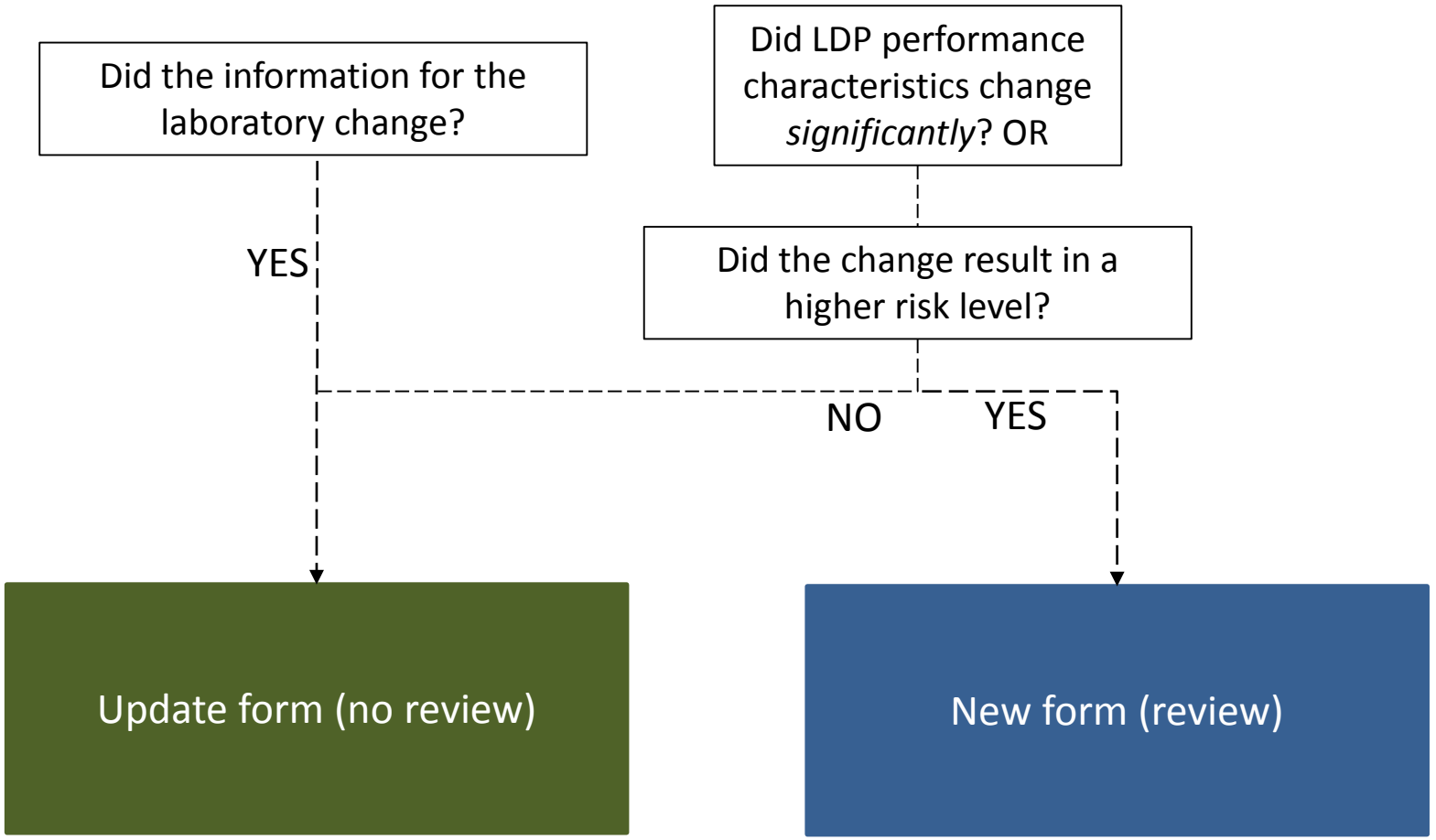
- Laboratories with demonstrated success with approved LDPs in the same or higher risk classification, will be conditionally approved to begin testing with LDPs that use similar technologies or methodologies pending the outcome of the review.

Modifications

Ensuring Quality

Preserving Innovation

Modifications to an Existing LDP



Expertise that advances patient care through education, innovation, and advocacy.

www.amp.org

AMP Association for Molecular Pathology

Modifications to an FDA Cleared/Approved IVD

- When an FDA cleared or approved IVD is modified **such that it alters the performance characteristics** established by the manufacturer it is considered an LDP
  - A laboratory is required to establish for each test system the performance specifications for performance characteristics
    - Performance characteristics as defined in the current CLIA regulations
  - Performance characteristics:
    - If changes do NOT alter the performance characteristics significantly, a laboratory is required to submit moderate and high risk LDPs for publication only
    - If changes alter the performance characteristics significantly, a laboratory is required to submit moderate and high risk LDPs for review and publication
  - Further modifications are subject to LDP modification requirements

Lab Inspectors & Inspection Process

- Require CMS to develop:
  - Minimum qualifications for inspector selection
  - Minimum requirements for inspector training
  - Consistent and ongoing training for inspectors
- Require relevant experts to inspect laboratories
- Require accrediting organizations to provide records to CMS on a yearly basis that include:
  - Any complaints, investigations, and conclusions regarding programs and services, and
  - Any corrective action taken
- Require that CMS establish a mechanism for laboratories to provide feedback to CMS on the inspection process

Updating CMS List of Analytes

- CMS has a list of analytes for which proficiency testing is required through an approved program
- Proposal creates a mechanism through which the list will be reviewed on a biennial basis and updated no less frequently than five years
  - Must utilize Advisory Board of specialty subject matter experts

Proficiency Testing or Alternative Assessment for ALL LDPs

Analyte on CMS list?	
YES	NO
Must participate in proficiency testing through a CMS-approved program, or through alternative assessment if a formal proficiency test does not exist.	A laboratory may choose whether to participate in external quality assessment through a CMS-approved program, or through alternative assessment.

Alternative assessment can involve:

- Conducting comparative testing using samples, specimens, contrived specimens that have been split between two individuals in the same laboratory, or
- Conducting comparative testing by exchanging samples, specimens, or contrived specimens with other laboratories.

Reporting Laboratory Errors: Current CLIA Regulations

- Current CLIA regulations require that each laboratory:
  - Report patient result errors to the authorized person ordering the test
  - Maintain a record of those errors
  - Ensure that all complaints and problems reported to the laboratory are documented
  - Conduct investigations of complaints when appropriate
  - Issue a corrected report
- Third Party Accreditors must notify CMS within 10 days of any deficiency identified in an accredited or CLIA-exempt laboratory if the deficiency poses an immediate jeopardy to the laboratory's patients or a hazard to the general public

Modifications to Regulations on Reporting Laboratory Errors

- Require labs to have **ready access to a mechanism for ordering physicians** to report possible laboratory/LDP errors
- Require that any investigations conducted by a laboratory that reveal an error poses immediate jeopardy to the laboratory's patients or a hazard to the general public **be reported to CMS directly**
- Require that CMS **provide this information to the public** through the database

Preserving Innovation: Life of an LDP

1. Development: LDP developed; lab classifies based on risk definition
2. Submission: Lab submits High & Moderate Risk LDP information to reviewer before offering the service to the public
3. Review: CMS/Third Party Reviewer reviews LDP information
   a. Timing based on risk classification
   b. CMS may reclassify risk; lab may appeal
4. Public Database: CMS creates publicly accessible entry for LDP
5. Decision: Review decision issued; lab may appeal
6. Post Introduction Monitoring: Lab participates in proficiency testing and is inspected
7. Adverse Event Reporting: LDPs that pose immediate jeopardy to the laboratory's patients must be reported directly to CMS
8. Modifications: Lab continuously improves LDP over time
   a. Depending on the modification(s), may require a new submission & review of LDP, OR solely updating the existing LDP form

Annual Fees

- CMS is allowed to require the payment of fees to facilitate activities for LDP oversight
- Commensurate with the number of LDPs
- Limited to cost recovery
- Reviewed and updates recommended by subject matter expert advisory board
- Fees outside of those standard for accreditation inspection waived for public health laboratories

Ensure Adequate Scientific Expertise

- Require that the CMS division responsible for the implementation of CLIA regulations have in its top leadership a board-certified professional who has served as a laboratory director in a clinical laboratory that performs high complexity LDPs, and understands the special considerations of complex LDPs and a wide range of different types of LDPs
- Require CMS to develop a mechanism whereby it can utilize the expertise of relevant subject matter experts in the medical and scientific communities

No Duplication of CLIA Requirements

Require that CMS:

- Insert the following text: "No State, tribal, local government (or political subdivision thereof), or government contractor may establish or continue in effect any requirement related to assessing the analytical and/or clinical validation of an LDP that is different from, or in addition to, the requirements of [the CLIA regulations as amended by this bill] for the purposes of assessing whether the LDP is reasonable and necessary, *i.e.,* for coverage and payment purposes."
- No federal government entity or entity that sets coverage or payment policy may be a CMS-approved Third Party Reviewer

Protocol Sharing

- Labs within a single corporate entity may share protocols without having to submit LDP information as long as the corporate entity controls and specifies all aspects of the LDP, *e.g.,* the instruments and reagents used, and the receiving laboratory verifies LDP performance
- CDC and public health laboratories may share protocols without having to submit LDP information as long as the receiving laboratory verifies LDP performance

Timeline

- Updated CLIA regulations will be finalized within two years after the legislation is enacted
- Requirements will be effective two years after regulations are finalized

Key Features

- Tiered; risk-based
- Regulates LDPs as professional services
- Assures both analytical and clinical validity without jeopardizing innovation
- Provides for rapid response during public health emergencies
- Provides transparency so physicians and patients have essential information
- Levels the playing field by applying the same regulatory principles to anyone who develops an LDP
- Provides for pre-introduction review of high & moderate risk LDPs
- Provides for enhanced standards
- Requires proficiency testing or alternative assessment for all LDPs
- Does not change states' exempt status under CLIA
- Avoids duplication of activities within and between federal agencies
- Provides for shared LDP protocols
- Timeline: 2 years to final rule; another 2 years after final rule to take effect