Regulation of Clinical Metagenomic Assays for Infectious Disease: Industry Perspective

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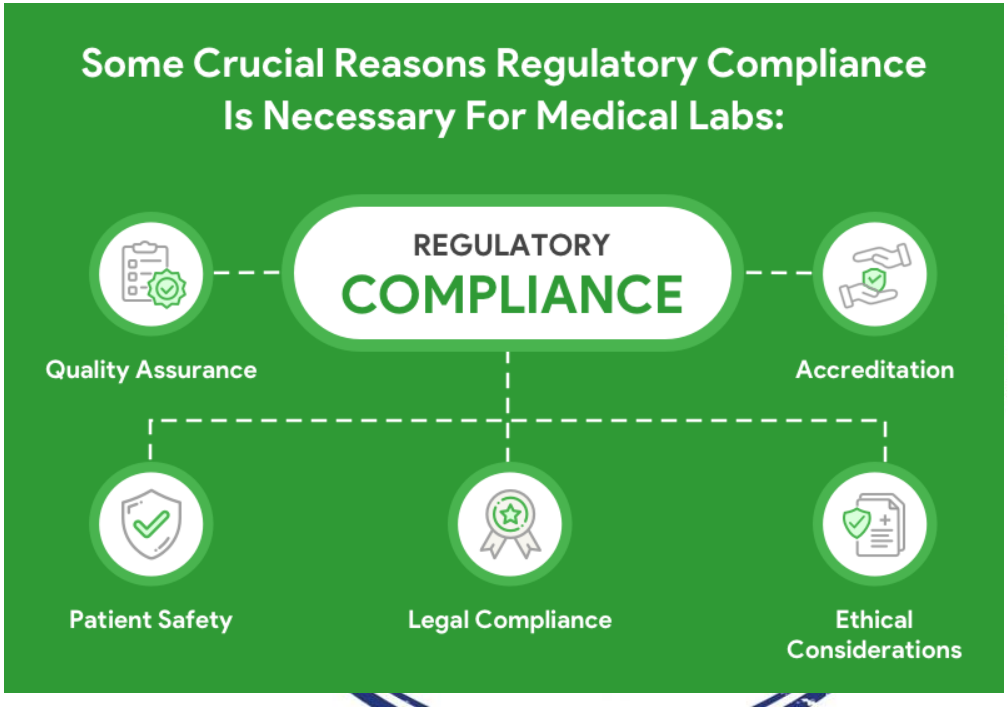
Disclosures

Employee and Shareholder, Delve Bio, Inc.

Multiple patents relating to mNGS pathogen detection

Clinical Laboratory Regulatory Framework



CrelioHealth: Regulations and Standards in Medical labs: Ensure Quality, Safety, and compliance

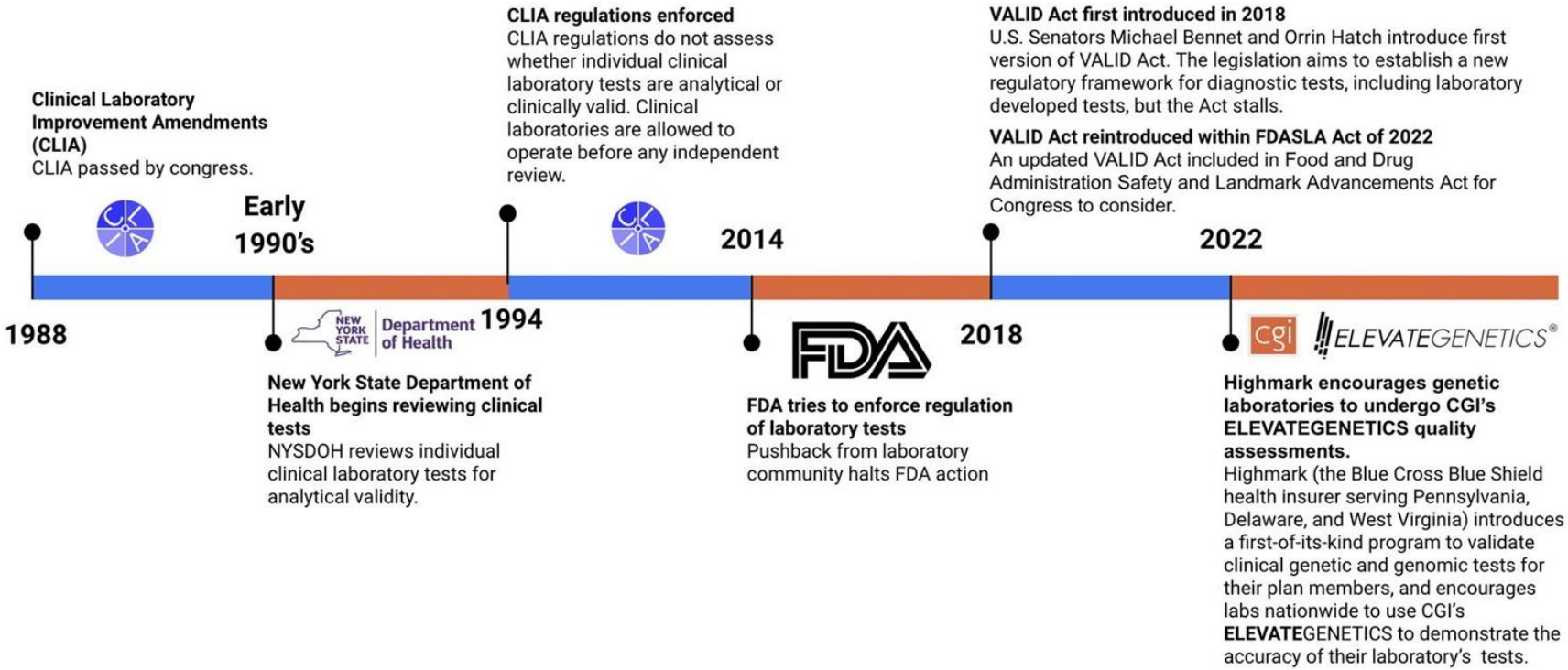
Global LDT Regulation

Variation in Regulatory Approach

- United States
  - CLIA / CAP, FDA enforcement discretion
  - Proposed FDA rule on LDTs
- EU - May 2022 IVDR
  - LDTs can be used until May 2028
  - Need to justify use of LDT as no comparable IVD available
- China - 2023 National LDT Pilot Regulations
  - LDTs allowed “under guidance of physicians” “within own entity” until IVD available
  - Once IVD registered, similar LDTs not allowed
  - LDT Registration appears not to be required
  - Companies offering LDTs to hospitals under current rule
- Others
  - Japan - no LDT framework, only IVDs reimbursed
  - Singapore - Draft LDT Guidelines
  - Variety of national regulations

Changes in US Regulatory Landscape

Center for Genomic Interpretation quality initiative



Pathway to IVD for Clinical Diagnostics

Variety of LDT to LDT pathways

Type of Testing

- LDT
  - Single lab, centralized testing model
  - Modification of IVD (sample, patient, protocol)
  - Analyte-specific reagents (ASR)
  - Lab-developed protocol
- IVD
  - Single-site approval
  - Protocol IVD
  - Testing kit components
  - Testing system
  - Point of care

Use Cases

- LDT
  - Esoteric, hard to perform tests not available as IVD
  - IVD not available locally
  - Cost control in reference laboratory
  - Lower validation and postmarket surveillance requirements
- IVD
  - Standardize across institutions
  - Commercialize test kits
  - Manufacture and distribute reagents, instrumentation

Industry Perspective on LDT Regulation

Pros

- Potential competitive advantage once approval obtained
- Several IVD required elements part of best practices
  - Design control
  - Risk assessment and mitigation
  - Postmarket surveillance
- Marketing as IVD-approved
- Ability to distribute test kits / systems

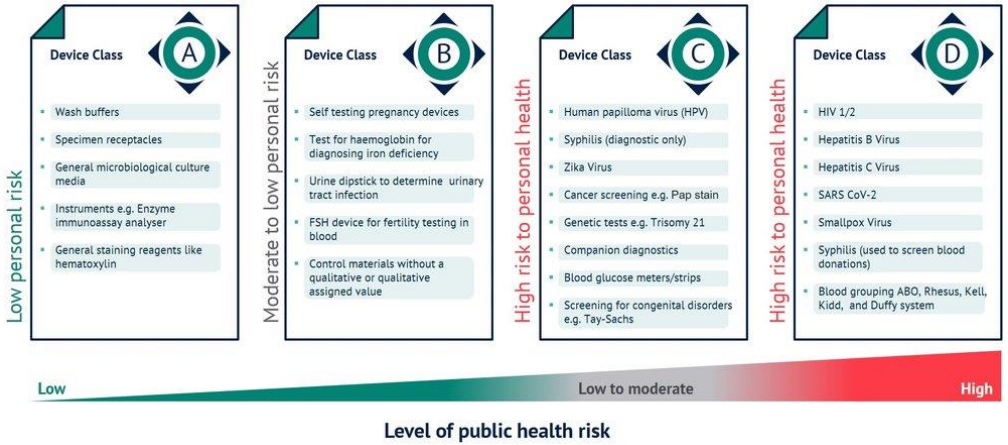
Cons

- Additional time and expense required to submit for IVD approval
- More difficult to update test methods as technology changes
- IVD approval not linked to reimbursement or inclusion in practice guidelines
- Uncertain outcome of regulatory review increases risk to company / investors

EU IVDR

Risk Classification

- Infectious disease diagnostic tests
  - Categorized by risk A-D (low-high)
  - Class D: donor screening, life threatening pathogens, viral load monitoring
  - Class C: Infectious disease screening, death or disability due to false result
  - Class B: Others
  - Class A: General laboratory use products

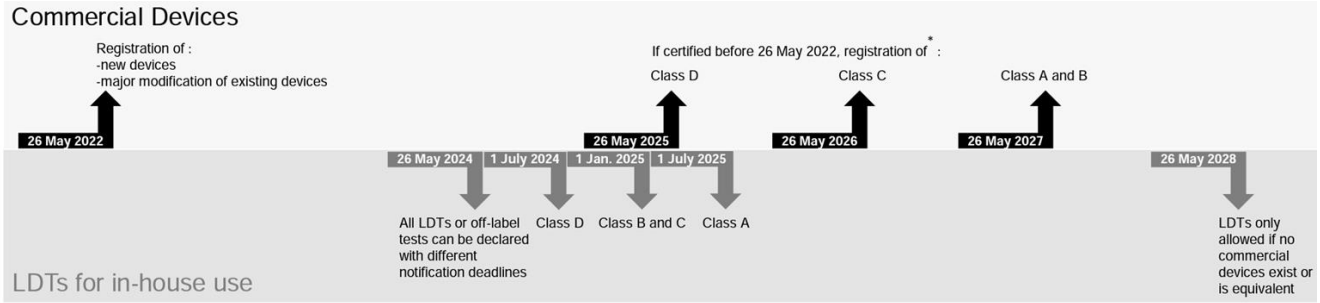


https://www.reg-metrics.com/blogs/what-are-the-new-device-classifications-in-the-in-vitro-diagnostic-regulation-ivdr/

EU IVDR

Regulatory Requirements

- Assignment of risk category
- Technical Documentation
  - Summary of product safety and performance uploaded to EUDAMED
  - Periodic safety update
- Implement QMS
- Manage Supply Chain
- Postmarket Surveillance
  - Safety and performance updates
  - Major incidents and corrective actions



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EU IVDR

Downsides of increased regulation

Table 4. Major potential risks for microbiology laboratories due to IVDR.

Risk	Reasons Foreseen
Costs	Increased workload; additional reagents and control costs
Reduction of quality	Less test diversity, fewer laboratories, less innovation, reduced capacity to rapidly react to emerging microbes, decreased skills of co-workers
Lack of tests	Decreased diversity of commercial tests and strong pressure against LDTs will increase the demand for the remaining commercially available tests
Loss of specialists	The regulatory burden and reduced scope for innovation may make the profession seem unattractive.

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- Similar effect to proposed FDA regulations
- Evidence that manufacturers are discontinuing tests for rare conditions
  - Coxiella and Bartonella IFA detection assays
- Dependence on fewer methods
- Restricted access
- Testing for emerging agents likely to be delayed

Major Reasons IVD Applications Not Pursued

Lab manager survey

	Total
Test is too low-volume to warrant filing for IVD	46%
Novel test—will eventually become IVD	45%
Test is evolving quickly (e.g., new markers)	43%
Test is instrument- and interpretation-based (e.g., mass spec, flow cytometry, immunohistochemistry)	35%
Filing for IVD would be too expensive	28%
Test is specific to a single lab/lab company and no desire currently exists to market it outside of lab/lab company	23%
Other	1%

Regulatory Effect for Metagenomic Diagnostic Assays

Market Effects

- Time to Market
  - Longer, more expensive pathway prior to launch
- Development Risk
  - Increased resources to build and maintain testing
- Market Consolidation
  - Fewer labs performing site-specific testing
  - Potentially higher volume for reference laboratories
- Focus on High Volume Tests
  - Infrequent tests have low potential for sufficient revenue to offset increased development costs

Industry Response to Regulatory Changes

Strategic Response

- Business strategy to include manufacturer activities
  - QMS documentation
  - Develop submission packets
  - Postmarket surveillance
- Plan for technology change
  - Reagent / chemistry modifications only on major updates
  - Bioinformatics update process for database changes
  - Cross-validation on multiple sequencing instruments / platforms
- Clinical utility data
  - Validations to include assessment of clinical utility
  - Involvement in trials to assess safety and efficacy
  - Protocols to include patient management decision algorithms

Validation Requirements for Metagenomics Assay

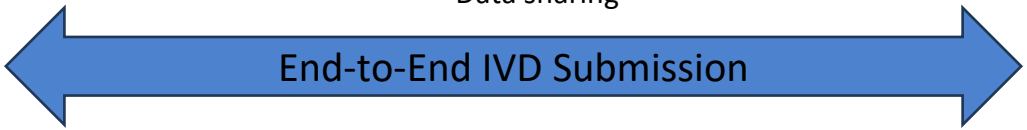
Comparison to MALDI

- LDT
  - Representative organism approach
  - Isolate banks exist for rare organisms
  - No similar banks for clinical samples containing rare organisms
- IVD
  - Each claimed species submitted in filing
  - RUO Database
    - May be used for individual lab as modified IVD (LDT)
  - Updates to Clinical Database
    - Significant number of samples / submission cost
- New validation approaches needed
  - Methods-based identification rather than organism-based
  - Risk of misidentification assessed
  - Confirmation for novel agents / atypical findings

Regulatory Implications for Metagenomics Assay

Number of Partners Needed to Develop and Perform Test

- Sample processing
  - Automation
    - Instrumentation, consumable supply
    - Validation of automated processing
  - Library preparation reagents
    - Quality, lot-to-lot variation
    - Nucleic acid contamination
    - Changes to kits
  - Sequencing
    - Instrument support, life cycle
    - New high-throughput sequencers
    - Reagent qualification for IVD
- Bioinformatics
  - Database
    - Periodic updates
    - Curation
    - Database size and computational requirements
  - Pipeline
    - Updates to alignment tools
    - Versioning
    - Process validation
  - Data Processing and Storage
    - Local vs cloud infrastructure
    - HIPAA / privacy requirements
    - Data sharing
- Reporting
  - Result Interpretation
    - Contaminant vs pathogen
    - Clinical significance
  - Public Health Reporting
    - Multiple jurisdications
    - Novel agents



Summary

Regulatory Changes Affecting Metagenomics

- Gaps in regulatory framework in process of being filled
  - Require good practices in design control, clinical validation, postmarket surveillance
  - EU IVDR already in place
  - FDA changes less certain but likely some review process (3rd party)
- Winners and losers from increased regulatory barriers
  - Market consolidation due to barrier to entry
  - Potential for decreased access / availability for low volume tests (orphan diagnostics)
- Regulators need guidance on best practices
  - Change control / updates to assay as technology advances
  - Validation best practices
  - Potential for regulatory-grade tools for that can be combined for metagenomics assays
    - Databases, pipelines, library prep workflows, etc