Laboratory Developed Tests (LDTs) and the FDA: The Impact on Clinical Laboratories

THSNA: Current Challenges in Coagulation

Curtis A. Hanson, M.D.
Professor of Laboratory Medicine and Pathology
Mayo Clinic – Rochester, MN
and
Chief Medical Officer
Mayo Medical Laboratories (MML)

April 15, 2016
Disclosures

Relevant Financial Relationship(s)
• None

Off Label Usage
• None
Today’s Outline

• Coagulation laboratories and LDTs
• FDA Guidances – what are they?
• What problems are the guidances supposed to solve?
• What has been the response to these guidances?
• What’s next?
• What should laboratories do to prepare?
Definition of LDT

- A LDT is any test, used in a single laboratory, that has not been approved or cleared by the FDA. This includes any FDA-approved or cleared kit that has been modified in any way by the laboratory. Modifications include, but are not limited to: changes in specimen stability, accepting different specimen types than what is listed in the package insert, any changes made to the procedures or reagents, etc.
Why should I pay attention today?

• Laboratory Developed Tests (LDTs) are critical to the practice of medicine regardless of the size of your laboratory

• FDA wants to regulate LDTs

• Regardless of outcome of the current initiatives, it is highly likely that we will see a major change in how LDTs are regulated

• We will all need to become more facile and knowledgeable about regulatory requirements – beyond CLIA and CAP!
Today’s Outline

• Coagulation laboratories and LDTs
• FDA Guidances – what are they?
• What problems are the guidances supposed to solve?
• What has been the response to these guidances?
• What’s next?
• What should laboratories do to prepare?
LDTs in the Coagulation Lab at Mayo Clinic

- ADAMTS13 Activity and Inhibitor
- Hemophilia A F8 Gene, Intron 22 Inversion Known Mutation
- Hemophilia B, Factor IX Gene Mutation Screening
- Plasminogen Activator Inhibitor Antigen
- Platelet Surface Glycoprotein by Flow Cytometry
- Platelet Transmission Electron Microscopic Study
- Ristocetin Inhibitor Assay
- Soluble Fibrin Monomer
- von Willebrand Factor Multimer Analysis,
- von Willebrand Disease 2N (Normandy) by PCR
# LDTs in the Coagulation Lab at Mayo Clinic: Modifications to FDA Kits

- 5,10-Methylenetetrahydrofolate Reductase gene mutations
- Factor V Leiden (R506Q) Mutation
- Prothrombin G20210A Mutation
- Antithrombin Antigen
- Heparin-PF4 Antibody (HIT)
- Factor Inhibitor and Bethesda Assays
- von Willebrand Factor Activity
- Reptilase Time
- Thrombin Time
- Platelet Neutralization Process (PNP)
- Protein S Total

| Coagulation Factor X Inhibitor Screen |
| Coagulation Factor XI Inhibitor Screen |
| Coagulation Factor II Activity Assay |
| Coagulation Factor V Activity Assay |
| Coagulation Factor VII Activity Assay |
| Coagulation Factor VIII Activity Assay |
| Coagulation Factor IX Activity Assay |
| Coagulation Factor X Activity Assay |
| Coagulation Factor XII Activity Assay |
Today’s Outline

• Coagulation laboratories and LDTs

• FDA Guidances – what are they?
  • What problems are the guidances supposed to solve? What issues…
  • What has been the response to these guidances?
  • What’s been happening recently?
  • What should laboratories do to prepare?
Background

• Draft Guidance issued by FDA on October 3, 2014
  • FDA Notification & Medical Device Reporting for LDTs
  • Framework for Regulatory Oversight of LDTs
Notification & Medical Device Reporting – Draft

Notification

• Once Guidance is finalized, 6 months to notify FDA with required information about LDTs, including FDA-modified assays.

• 14 data elements required
  • E.g., Intended use is a big one
  • E.g., Clinical use of test (e.g., diagnosis, prognosis, monitoring, risk assessment, screening, etc.)

Medical device reporting

• Adverse event reporting required within 30 days of event – may have caused or contributed to a death or serious injury. Or malfunctioned leading to…
Framework for Regulatory Oversight – Draft

- Assure that LDTs are “safe and effective” (analytical validity and clinical validity)
- Risk-based classification – low, medium, high (I, II, III)
- Forensics and histocompatibility excused
- Can’t offer LDTs outside your facility – only if FDA-approved
- Can’t offer moderate or high risk LDTs until you have FDA-approval
- PMAs and 510Ks have been the standard requirement for class III (high) and class II (moderate) devices, respectively
- Design Controls, Quality System Requirements
- 9 year phase-in process
- Modifications are LDTs
- No grandfathering
Draft FDA Guidances

• The intent of the guidances is perhaps admirable and there are LDTs that need to be fixed.

• However, the unintended consequences of the guidances – as currently written – will have a significant and deleterious impact on the practice of medicine and on our ability to provide patient care.

• Remember: estimated that there are greater than 100,000 LDTs in the US
Impact on Academic-based Laboratories

- Slow innovation. Submission requirements are substantial. Also, if you have to stop offering an LDT when an alternative is on the market, then limited incentives to bring discovery to the bedside.

- FDA-approved kits are frequently not better – especially when there are few in the market: e.g., Tacrolimus, ALK, BRAF, KRAS

- Financial costs are not trivial; submission costs and additional internal administrative costs will limit the number of LDTs that can get done; difficult to get resources

- Submissions for FDA kit modifications will inhibit bringing new discovery to fruition as modifications can: Improve process; add different specimen types; offered across different tumor types; etc.
Final FDA Guidances???

- All indications are that the final guidances will be released in the 2nd Q 2016
- Final guidances – what will the content be???
- Very hard to plan as we don’t know what will be in the final guidances
- It is likely that they will address some of the issues that have been raised by laboratories – but don’t expect there to major revisions or major changes in direction
- There will a long phase-in time period
- FDA wants to work with clinical laboratories in making this work – education will be critical
Today’s Outline

• Coagulation laboratories and LDTs
• FDA Guidances – what are they?
• What problems are the guidances supposed to solve?
• What has been the response to these guidances?
• What’s next?
• What should laboratories do to prepare?
20 Case Studies Presented by FDA

- Lyme disease diagnostic tests
- OvaCheck ovarian cancer screening and detection test
- OvaSure ovarian cancer screening test
- PreOvar KRAS-variant ovarian cancer screening test
- Whooping cough (pertussis) diagnostic PCR test
- Oncotype DX HER2 breast Cancer RT-PCT test
- Human papillomavirus test using SurePath collection medium
- Fibromyalgia FM/ a diagnostic test
- Noninvasive prenatal testing cell-free DNA testing)
- KIF6 genotyping test to predict heart disease risk and statin RX response
- Target Now cancer biomarker test
- Polaris prostate cancer biomarker test
- Chronic fatigue syndrome XMRV test
- CARE clinics autism biomarkers test
- Heavy metal chelation challenge test
- Omapro companion diagnostic to new leukemia medication
- Duke University chemotherapy assessment test
- Vitamin D deficiency test
- OncoVue genetic breast cancer risk test
- BRAFV600E genetic mutation test to guide melanoma treatment
20 Case Studies Presented by FDA

Examples used by FDA

• Incorrect diagnoses of ovarian cancer
  • – Led to unnecessary surgeries to remove ovaries

• Incorrect prediction of tumor types (Duke Univ. Study)
  • – Exposed some patients to ineffective therapies
  • – Left other cancer patients untreated

• Incorrect diagnoses of whooping cough
  • – False whooping cough epidemic at Dartmouth medical center
  • – Thousands given unnecessary antibiotics and/or vaccine
  • – 1,000 healthcare workers furloughed
FDA’s stated need for oversight of LDTs

- Lack of evidence supporting the clinical validity of tests
- Intended use and how validation addresses that or not
- Deficient adverse event reporting
- No premarket review of performance data by outside reviewers
- Companion diagnostics require specific tests linked to those specific drugs
- Unsupported claims made by the laboratory
- Inadequate information provided to patients and providers
- Lack of transparency – data not shared; is it an FDA-approved/cleared or an LDT
- No comprehensive listing of all LDTs currently being used
- Use of LDTs in clinical trials may compromise the results
- Screening tests require a different validation approach
Patient Advocacy Groups

• Patient groups do not understand the labs and what we do

• Their general belief is that only the FDA can assure safety and effectiveness

• Patient groups are demanding that FDA control LDT testing

• The “FDA 20” includes some tests that have been the focus of particular patient disease advocacy groups
Current standards are ineffective for oversight

- It is too easy to get a CLIA-only certificate
- Incomplete standards for LDTs – especially if accreditation is outside of CAP
- Niche laboratories not associated with a clinical practice cannot demonstrate the same level of clinical validation
- Variation amongst labs on how to do test development
- May use inappropriate controls for validation studies – using “normals” that are not based on the intended use
- Variable understanding of positive and negative predictive values with a LDT and how results should be reported
So are most labs a problem? NO!!!

- Mayo Clinic reports and collects all sentinel events related to patient safety and adverse, unexpected outcomes.
  - Submitted by patients, employees, or physicians
  - Evaluated by an institutional sentinel event office
  - We use this same process with our MML clients.
- Over the last 6 years:
  - 2.5 million LDTs for Mayo Clinic patients
  - 0 sentinel events related to the design or validation of LDTs
  - 19 million LDTs for MML clients
  - 0 sentinel events related to the design or validation of LDTs
- Mayo and our experience is not unique!
Today’s Outline

• Coagulation laboratories and LDTs
• FDA Guidances – what are they?
• What problems are the guidances supposed to solve?
• **What has been the response to these guidances?**
• What’s next?
• What should laboratories do to prepare?
What’s Next? – ACLA

- American Clinical Laboratory Association (ACLA) may or may not file the lawsuit once FDA finalizes the guidance documents for LDTs – uncertain
  - Will cause delays
  - Unlikely to be a long term solution
  - Even if suit was in favor for ACLA, FDA could turn around and implement via rule-making process
- Recent unanimous Supreme Court decision ruled that Department of Labor could issue major changes via guidances instead of going through rule-making
What’s Next? – CLIA

• Almost zero hope that CLIA will step in and take charge

• CLIA has said it will not regulate LDTs – deferring to FDA
  • Analytical validity requirements in CLIA and CLIA does not address clinical validity

• CLIA states that it “regulates laboratories to ensure accurate and reliable test results when laboratories perform testing on patient specimens”

• Both House E&C and Senate HELP validated there is no hope that CLIA will be enhanced for LDTs – CLIA has no interest

• Regardless of jurisdictional issues, CLIA needs to be updated
What’s Next? – Diagnostic Test Working Group (DTWG)

• DC law firm brought together labs and IVD companies; started with “clean sheet of paper”
• New FDA Center sole & exclusive jurisdiction over In Vitro Clinical Tests (IVCTs) test development activities; IVCTs would not be regulated as a device, drug or biologics
• Activity based framework, same activities regulated in the same manner
• Tiered, risk-based approach for oversight based on risk to the patient and whether testing is well characterized
• Safety and effectiveness standard measured as analytical validity & clinical validity
• Post-market surveillance and adverse event reporting in all high risk testing
• Modifications limited to whether there has been a meaningful clinical impact or changes to the intended use
• Grandfathering of LDTs pre-enactment
• Special categories for rare disease, emergency use and unmet needs
Function | Activities | Jurisdiction
---|---|---
Test Development | • Design  
• Development  
• Validation  
• Protocol | FDA
Laboratory Operations | • Develop lab SOP  
• Verify lab performance  
• Pre-analytical  
• Perform the test  
• Report the results  
• Proficiency testing  
• Adverse event reporting | CLIA
Medical Practice | • Interpretation  
• Consultation  
• Medical relevance | States
Will the DTWG Proposal Succeed?

- Unsure – Congress is not known for progress.

- Would have to go through the legislative process in the House – “21st Century Cures” bill.

- Would have to get through the legislative process in the Senate – “Innovation for Healthier Americans” bill.

- Combine and pass?? President to sign?? Whose president?

- Does put further political pressure on FDA to hold off on issuing guidances. Does give FDA a different framework from which to modify the guidances.
AMP, AMA, CAP, and Others

- AMP has offered a very loud voice in opposition to the FDA guidances and to the DTWG proposal.
- AMA has been trying to pull together medical societies and offering compromise solutions to the guidances.
- CAP has stated that it already put out its proposal in 2010.
- All three are variations of CLIA-centric solutions.
- None appear to have any traction at the current time in DC; AMA may have the best vision as to offering an alternative solution.
Today’s Outline

• Coagulation laboratories and LDTs
• FDA Guidances – what are they?
• What problems are the guidances supposed to solve?
• What has been the response to these guidances?
• What’s next?
• What should laboratories do to prepare?
What’s next?

• All indications are that the final guidances will be released by FDA in the 2\textsuperscript{nd} Q 2016.

• I hope I’m wrong…
What’s Next? – Statutory/Legislative

• Statutory/Legislative Approach to LDT oversight & regulation would supersede FDA Draft Guidance
  • House Energy & Commerce 21st Century Cures bill – Placeholder for LDTs
  • Senate HELP – Innovation for Healthier Americans bill

• Diagnostic Test Working Group (DTWG) – legislative language is being incorporated into 21st Century Cures bill; 3rd revision of draft legislative language being submitted this month / early next

• Lab organizations (AMP, AMA) have expressed opposition to the DTWG’s proposal in the E&C
Today’s Outline

• Coagulation laboratories and LDTs
• FDA Guidances – what are they?
• What problems are the guidances supposed to solve?
• What has been the response to these guidances?
• What’s next?
• **What should laboratories do to prepare?**
What will clinical laboratories need to do in a new “FDA” world?

• Hoping the status quo will be the outcome is not a plan
• The new reality is that there will be increased regulation of LDTs and FDA will likely be a part of that process
• Laboratories will have to make hard choices
What will clinical laboratories need to do in a new “FDA” world?

- Identify all your LDTs – including modifications
- Make an initial risk classification assessment of all your LDTs; high risk tests will be more costly to develop and submit
- Identify those LDTs that can be replaced by FDA-approved or cleared kit
- May have to make hard financial decisions – can you afford to offer LDT’s based on the costs and volumes?
- May need central oversight of LDT development to assure consistency and conformance to regulatory standards
How Can Laboratories Respond?

• Need a quality system that reaches back to the planning and development stage
• Need a system for defining, documenting and implementing standardized processes for test development
• Planning, organizing, and documentation is critical. Example:
  • Development plan
  • Locked-down analytical method prior to validation
  • Validation plan
  • Validation data – standardized
  • Validation summary
• Develop expertise and resources in submitting regulatory paperwork, e.g., clinical validation, PMA’s, and 510K’s
• Develop robust adverse event reporting system
• Keep test performance information in an electronic test catalog that will allow easy access by all
Questions?